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Mean Circadian Cosinors of Vital Signs, Performance of Blood and Urinary Constituents in Patients With Leprosy [1, 2]

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In healthy subjects, many body functions demonstrate a circadian rhythm and show a daily peak that occurs at a characteristic time during a 24 hour period. Heretofore, medicine has been based largely on the diagnosis and treatment of disease by comparison to rhythm-unqualified norms. Our position is that temporal aspects of normalcy and disease should be resolved and their relevance to medicine scrutinized. Studies should be aimed at describing and controlling or quantifying the properties of time-dependent variation, including circadian rhythms. Such knowledge presents new possibilities for disease detection and therapy based on changes in characteristics of rhythms ([2]).

The study described herein demonstrates circadian rhythms in a variety of behavioral, biochemical and biophysical variables in patients with leprosy. The results warrant examination of more extensive data series for deviations of rhythm characteristics in such patients as compared to healthy individuals.

During a ten day span from 06:00, Wednesday 20 August 1969, to 06:00, Saturday 31 August 1969, eleven volunteer subjects contributed data in four categories: 1) performance variables, 2) vital signs, 3) urine, and 4) blood. Ten subjects were patients with lepromatous leprosy, the eleventh was a presumably healthy medical student—an evaluation admittedly based only on the absence of known disease during sampling as well as the year following the study and on a physical examination at one year after sampling.

Six patients had inactive leprosy and four had active disease. In Table 1 each patient's hospital number, initials, age and weight immediately before and after the ten day span, type of leprosy, and activity of the disease are shown, along with pertinent information on the presumably healthy subject. All subjects were male, 23 to 66 years of age.

Classification of the disease as being active or inactive is based upon two indices, one bacterial (BI), the other morphologic (MI). These indices were rated by the number and forms of *Mycobacterium leprae* present in scrapings from skin.

Scrapings were collected from six standard sites: the two earlobes, elbows and knees. Smears of tissue fluid obtained by a superficial incision into the skin were stained with hematoxylin and eosin and Fite's acid-fast staining methods. The BI is rated according to the semiquantitative scale indicated in Table 2.

The MI (expressed in percent) is the ratio of the number of uniform intense-staining solid forms of the intact bacilli to the total number, including the fragmented and granular forms. An index of 1, 5 or 9 [or any other number] signifies the percent of solid forms noted among all forms counted. All these patients had a MI of zero. This zero MI indicates that even where the disease is active it is well controlled with medication, since the solid forms suggest viable organisms and the nonsolid forms nonviable ones.

All patients were receiving specific drugs for treatment of leprosy along with other

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TABLE 1. *Some characteristics of subjects investigated.*

Disease status[a]	Subject initials & number	Age (years)	Weight (lbs)		Bacterial Index
			before study	after study	
None	CR	23	155	152	—
Inactive	JA 2885	29	156	152	Zero
"	HP 2998	35	158	155	"
"	AH 2921	50	133	129	"
"	CC 2334	50	156	157	"
"	AG 2174	57	173	172	"
"	RH 1810[b]	66	145	135	"
Active	NL 2684	36	243	247	Zero[c]
"	AC 2453	48	198	199	4–5+
"	RG 2793	62	182	181	3+
"	JG 2926[b]	64	109	109	4–5+

[a]Disease: lepromatous leprosy. Morphologic Index zero in all cases.
[b]Restricted to a wheel chair.
[c]Classified as active since patient had not been negative for 12 consecutive months.

TABLE 2. *Rating of Bacterial Index (BI); bacteria in an average microscopic field.*

BI		
0	none	no bacilli seen
1+	rare	1–10 bacilli (100 F)
2+	very few	1–10 bacilli (10 F)
3+	few	1–10 bacilli/F
4+	moderate	10–100 bacilli/F
5+	numerous	100–1000 bacilli/F
6+	very numerous	over 1000 bacilli and clumps of bacilli/F

medications; none had received corticosteroids for the preceding six months. Patients were asked not to smoke, drink hot or cold beverages, eat or exercise during the 30 minute span prior to measurement sessions; any known deviation from these instructions was to be recorded before each examination in order to eliminate questionable data. Unknown transgressions seem unlikely, but cannot be ruled out. Each patient was given an approximately 2,140 calorie diet daily consisting of 218 grams carbohydrates, 92 grams protein, and 100 grams fat, as illustrated in the following example:

	Carbohydrates		Proteins		Fat	
	gm	cal	gm	cal	gm	cal
Breakfast	69	276	21	84	40	270
Dinner	79	316	42	168	45	405
Supper	70	280	29	116	25	225
Daily Total	218	872	92	368	100	900

MATERIALS AND METHODS

Performance testing. Examination of vital signs and urine sampling was repeated during wakefulness at three hour (± 10 minute) intervals. A sleep span of 8½ hours was uninterrupted on all days but the last one. Blood was sampled consistently at three hour (± 10 minute) intervals, day and night for the last 24 hour subspan.

The following performance tests were made:

1. *Short-term memory "forward" and "backward" test.* A series of numbers were read to each patient from a random numbers table starting with three numbers and progressively increasing by one number. The patient had to repeat these numbers in both the forward and backward number sequence. The recorded score indicates the highest number of figures repeated by the patient. Two scores were obtained in each session, one score for the forward series, another for the backward reproduction. If the patient was unable to repeat the initial three numbers, the score was zero.

2. *Eye-hand skill test.* A modified Stromberg Manual Dexterity Test was used with three rows of a test board. Twenty-seven holes were to be filled with diversely colored wooden discs. Discs were inserted in sequence as fast as possible without regard to the color of the disc. The time required for inserting all 27 discs was recorded in seconds.

3. *Grip strength.* A Jamar adjustable dy-

namometer was used. The patients were sitting during this test since some were unable to stand. The dynamometer was held firmly, first in the right hand. With the arm extended downward at about a 30° angle from the body, the dynamometer was squeezed as hard as possible. The value was recorded by the examiner and the procedure was repeated with the other hand. The subject remained unaware of the values; realization of a decreasing or increasing trend may well alter the outcome of each succeeding test.

4. *Random numbers addition test.* Consecutive numbers in a single column of 50 random numbers were added. The number of errors was recorded as the score for this test. The test was conducted in the language most familiar to the patient, English or Spanish.

5. *Physical vigor and mood.* These were rated by the testing personnel on the basis of observations and questioning of the subject. The following scale was used for mood rating: 1) blue; 2) somewhat depressed; 3) slightly less cheerful than usual; 4) usual state; 5) slightly more cheerful than usual; 6) quite cheerful; 7) happy, elated. An analogous scale ranging from "inactive, tired" to "active, full of pep" was used to rate vigor.

Vital signs. Oral temperature, blood pressure, pulse and peak expiratory flow were measured at three hour intervals from 06:00 to 21:00 each day as noted earlier; blood pressure and pulse also were taken on the tenth day during the entire 24 hour span.

1. *Oral temperature.* The thermometer was shaken until it read below 96°F and was then placed as far back under the tongue as possible. It was left in position with mouth closed for five minutes while other measurements were being taken. The temperature was recorded to the nearest tenth degree F.

2. *Blood pressure.* A mercury manometer was used. The cuff was wrapped around the left arm (all subjects were right-handed).

3. *Pulse.* Counted at the wrist for one full minute, using a stopwatch.

4. *Peak expiratory flow (PEF).* A Wright Peak Flow Meter was used, with subjects assuming the upright military stance except for the two wheelchair patients who performed the tests in a sitting position. The instrument was held with both hands, with dial facing vertically and the indicator at zero. The individual inhaled as deeply as possible in a short, sharp blast. The indicator reading was recorded as accurately as possible.

Blood sampling. Blood was collected in two 15-cc B-D vacutainers and centrifuged to obtain 10 cc of serum for the analysis of thirteen variables, as follows: transaminase, urea N., calcium, phosphorus, bilirubin (total and direct), chloride, cholesterol, creatinine, glucose, alkaline phosphatase, potassium, total protein and triglycerides. Additional blood was collected in a test tube containing 20-30 mg of ascorbic acid for serum 5-hydroxy-tryptamine determination. All specimens were centrifuged and the serum immediately frozen for storage at -50°C. The following methods were employed for the chemical analyses of the blood variables, as listed in part in Table 3.

Sodium and potassium: By flame emission on the IL 143 Flame Photometer internally referenced against lithium. *Calcium:* Fluorometrically on the Turner 111 Fluorometer, by method of Kepner and Hercules. *Chloride:* Coulometrically on the Buchler Chloridometer by method of Cotlove. *Total protein:* By photometric biuret reaction, method of Weichselbaum. *Cholesterol:* By photometric determination by method of Abell. *Triglycerides:* By automated colorimetric analysis performed on Auto-Analyzer I. Unpublished method of the Center for Disease Control, based upon the method of Carlson. *Alkaline phosphatase:* By Auto-Analyzer I, N-6a method; units coincide with conventional King-Armstrong units. *Bilirubin, total and direct:* By Auto-Analyzer I, N-12a method. *Glucose:* By Auto-Analyzer I, N-2b method. *Urea Nitrogen:* By Auto-Analyzer I, method of Mather and Roland. *Phosphate:* Auto-Analyzer I, N-4b method. *Creatinine:* Auto-Analyzer I, N-11b method. *SGOT:* By an automated version (CDC, adapted to Robot Chemist) of the method of Sax and Moore.

Urine collection. Urine was collected at three hour intervals from 06:00 to 21:00 with a nine hour span at night. Thus, six specimens were collected daily for ten days. The volume and temperature of the urine were recorded at each voiding, temperature to the nearest tenth degree. Voiding was directed upon the thermometer fixed within a receptacle at about 10 cm from the meatus. The specific gravity and pH were also measured

TABLE 3. *Chemical analysis of blood variables.*

Cholesterol	mg/100 ml	Ethanol-alkaline saponification; extraction into hexane; Lieberman-Burchard colorimetry.	Abell *et al.* J. Biol. Chem. **195** (1952) 357.
Triglyceride	mM/liter	CDC Auto-Analyzer method, adapted from Carlson and Lofland. Chloroform extraction with silicic acid adsorption of phospholipids; ethanol-alkaline saponification; automated oxidation to formaldehyde and colorimetric estimation with chromotropic acid.	Carlson. Atherosclerosis **3** (1963) 334. Lofland. Anal. Biochem. **9** (1964) 393.
SGOT	32° units	CDC automated (Robot Chemist) colorimetric assay of liberated oxalacetate with Azoene Fast Red. (The 32° unit is equivalent to 1.5 25° Karmen units.)	Sax and Moore. Clin. Chem. **13** (1967) 165.
Alkaline Phosphatase	Kind-King units	Auto-Analyzer N-6 method. Twelve minute reaction with phenyl phosphate; colorimetric estimation of liberated phenol with 4-amino antipyrine.	Kind and King. J. Clin. Pathol. **7** (1954) 342.
Bilirubin	mg/100 ml	Auto-Analyzer N-12a version of Jendrassik diazotized sulfanilic reaction; colorimetric measurement of "diazo blue." CDC "direct" assay, five minute color development.	Jendrassik and Grof. Biochem Z. **297** (1938) 81. Gambino. *Standard Methods of Clinical Chemistry*, vol. 5.
Glucose	mg/100 ml	Auto-Analyzer N-2a method; reduction of alkaline ferricyanide after dialysis.	Hoffman. J. Biol. Chem. **120** (1937) 51.
Urea-N	mg/100 ml	CDC Auto-Analyzer vertion of diacetyl monoxime reaction, linearized with thiosemicarbazide.	Mather and Roland. Clin. Chem. **15** (1969) 393.
Phosphate-P	mg/100 ml	Auto-Analyzer N-reaction with molybdic acid and reduction with aminoaphthol sulfonic acid.	Fiske and Subbarow. J. Biol. Chem. **66** (1925) 375.
Creatinine	mg/100 ml	CDC Auto-Analyzer version of Folin's Jaffe reaction (alkaline picrate).	Folin and Wu. J. Biol. Chem **38** (1919) 81.

for each specimen. Two 60 ml and one 30 ml samples of urine were collected on each occasion. Sodium metabisulfite was used as a preservative in the larger bottle of urine collected for catecholamine determinations. The 30 ml specimens served for analysis of 17-ketogenic steroids and electrolytes (Na, Cl and K). All specimens were immediately frozen and stored at -50°C until analysis. The urinary 17-ketogenic steroids were determined by a nonautomated procedure as employed by the Chronobiology Laboratories at the University of Minnesota Medical School. Potassium and sodium were determined by the Flame Photometer, Model 143, Instrumentation Laboratory, Inc., Boston, and chlorides were determined by the Buchler-Cotlove Chloridometer, an automatic titrator.

Data processing. All of the time series were transferred to punch cards and were processed first by the least squares fit of cosine functions with periods ranging from 28 hours to 20 hours, i.e., by linear least squares spectra. Such "windows" were prepared on each time series as a whole for each of the vital signs, behavioral, urinary and blood variables. Chronobiologic profiles were done next to check on the consistency of a circadian rhythm in the series. These analyses of individual series were followed by the application of the cosinor method. All methods have been described elsewhere ([1]).

Once a rhythm is detected, e.g., by cosinor, one can proceed to parameter estimation. A measure of timing is the computative acrophase, ϕ, shown for example in Figure 1. It locates the peak of the cosine

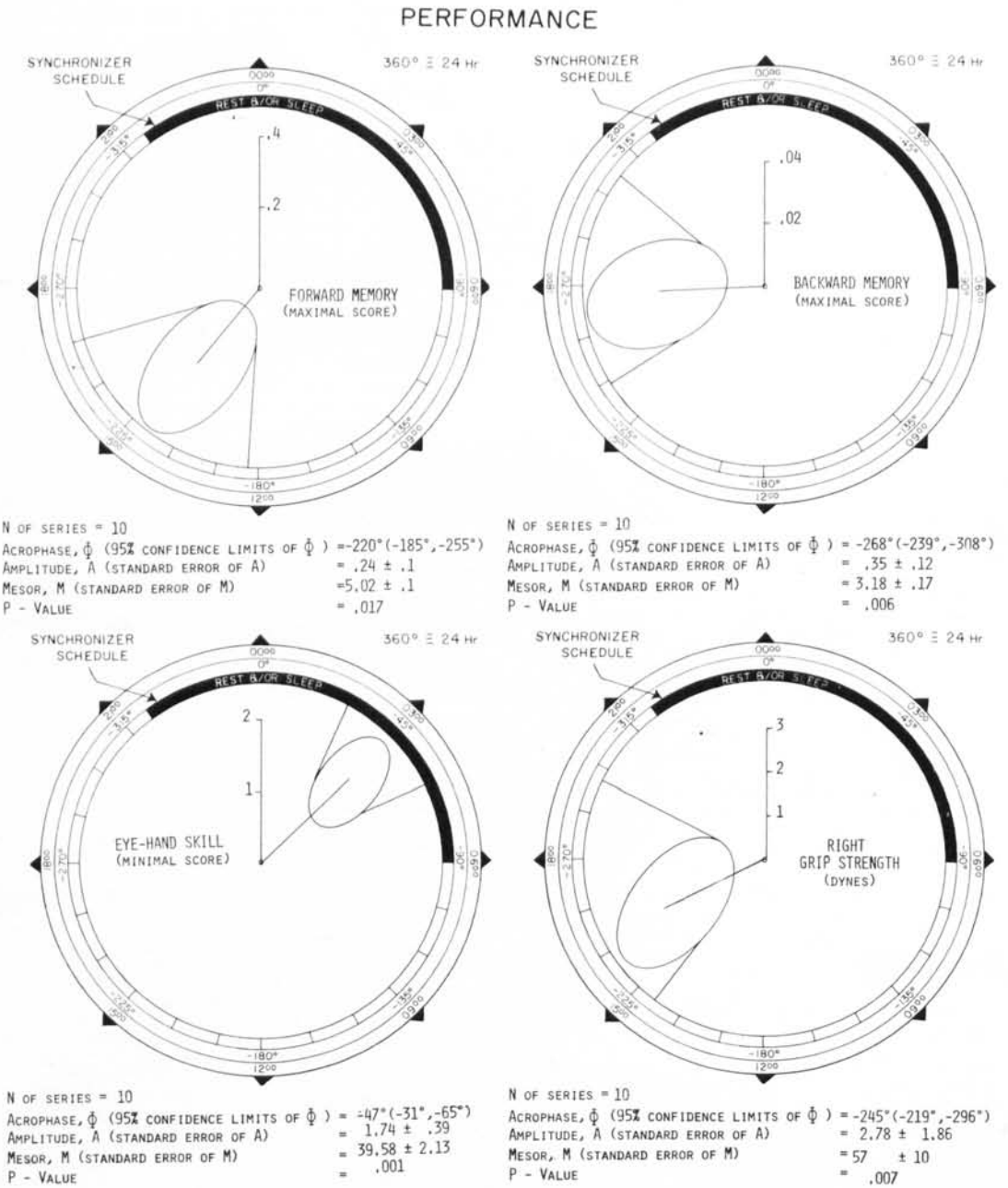

FIG. 1. Performance.

curve best approximating all data. ϕ may be expressed as a delay (denoted by a negative sign) from local midnight, with 360° = 24 hours; hence 15° = 1 hour. For example, the ϕ for the backward memory test (Fig. 1) as an indicator of the best time of mental performance is found about 18:00, i.e., at -268°, its 95% confidence arc extending from -239° to -308°.

RESULTS

Performance. Performance tests documented by relatively long data series were analyzed by the mean cosinor [1,2] following the fit of a 24 hour cosine curve by least squares to each individual series. Statistically significant circadian rhythms in two kinds of tests for short-term memory and in

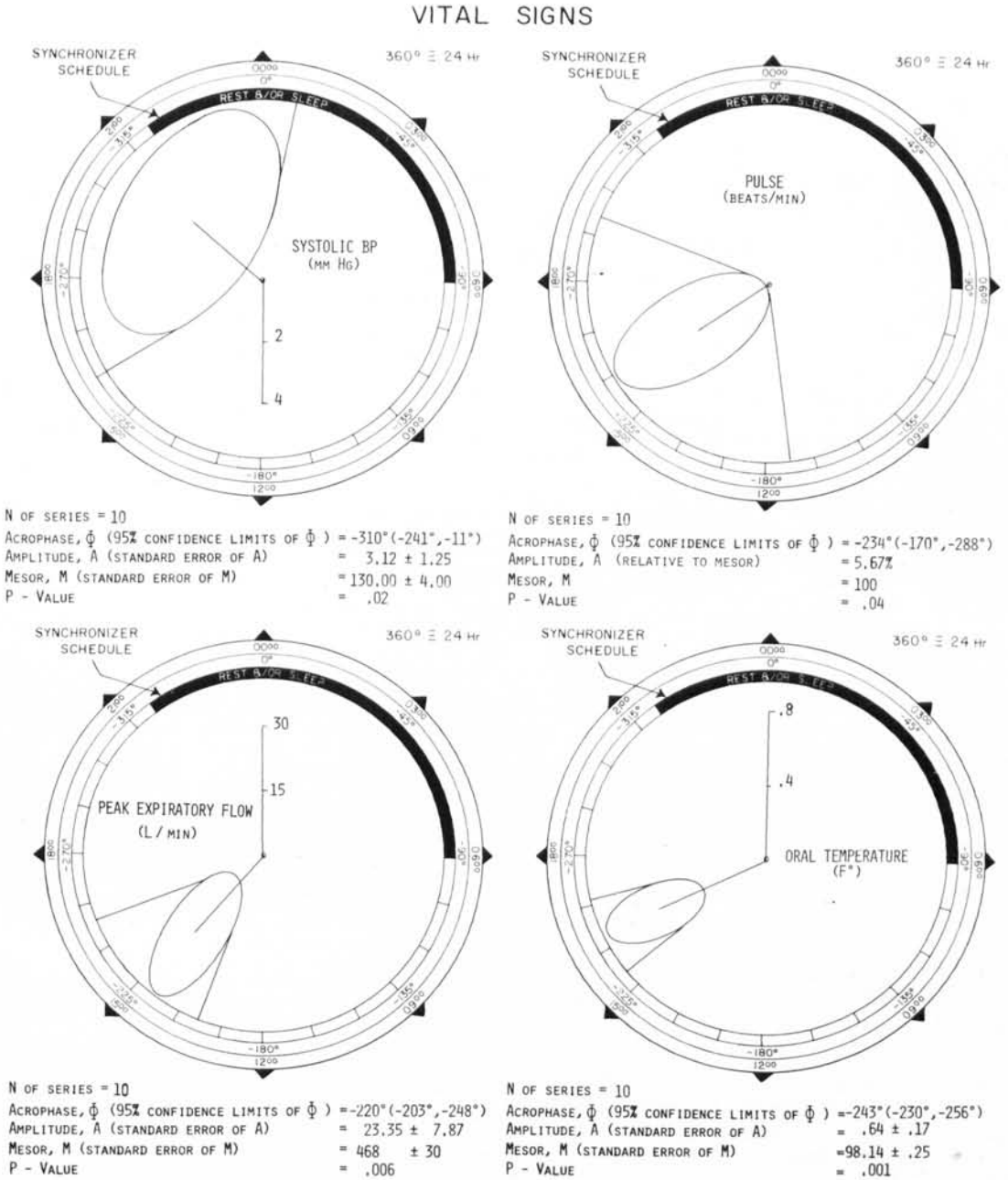

FIG. 2. Vital signs.

eye-hand skill and right-hand grip strength were found below the 2% level for all four variables—as indicated at the bottom of each cosinor plot in Figure 1 and as can be seen also from the four (elliptical) 95% confidence regions which do not cover the pole. A rhythm statistically significant at the 5% level was not detected in the samples on hand with the cosinor test for random number addition, physical vigor or mood ratings.

Vital signs and related variables. A circadian rhythm was detected at the 5% level of statistical significance or below, in oral temperature, pulse, systolic blood pressure and peak expiratory flow (Fig. 2). A cosinor test did not detect a statistically significant rhythm at the 5% level for diastolic blood pressure, although the p value obtained for

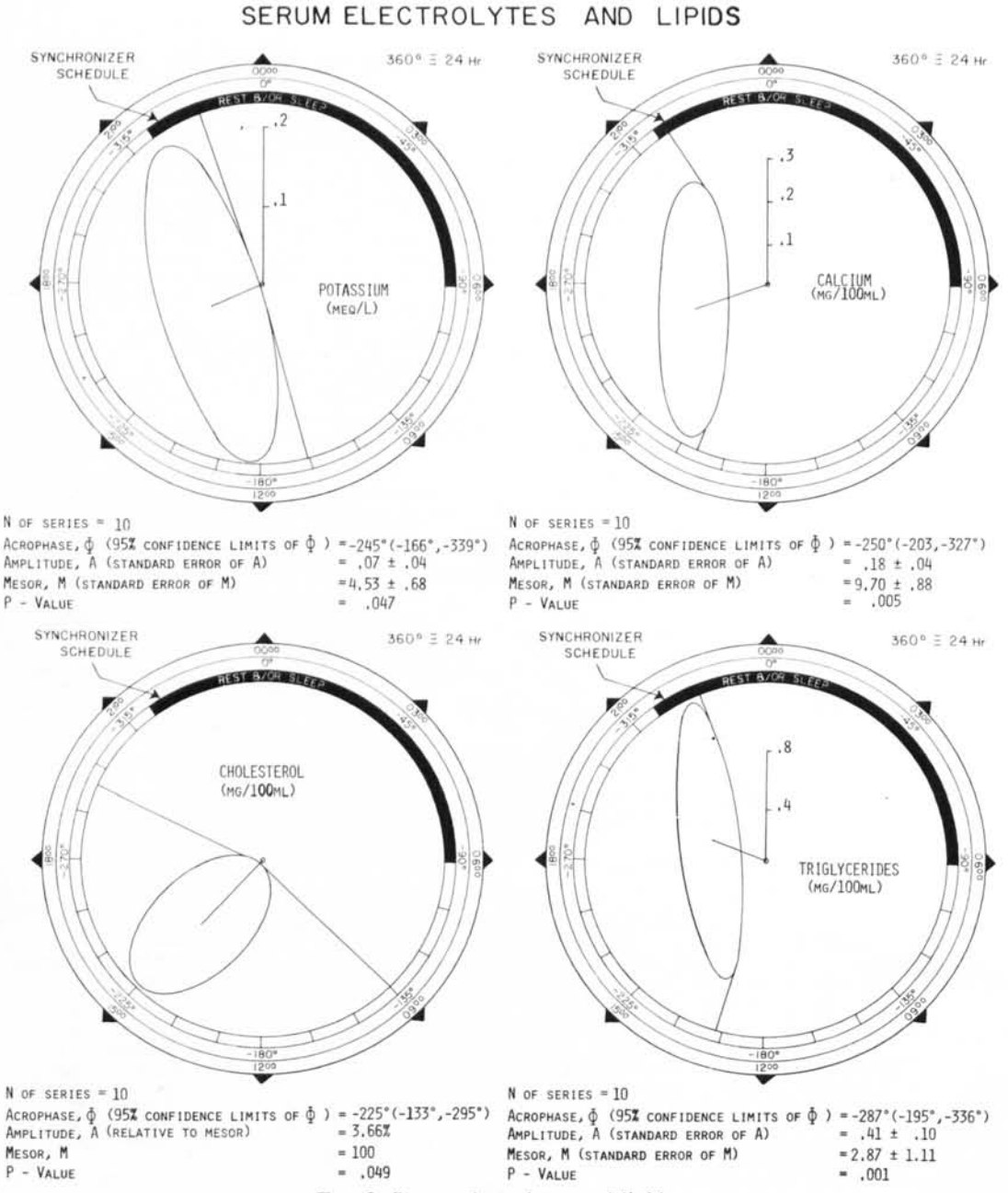

FIG. 3. Serum electrolytes and lipids.

possibly rhythmic circadian variation reached the 10% level.

Blood. Sampling of human blood at three hour intervals over a single 24 hour span allowed the demonstration of several circadian rhythms by the cosinor method. Rhythms significantly below the 1% level or at least below the 5% level were found for SGOT, alkaline phosphatase, total as well as direct bilirubin, cholesterol, triglycerides, urea, potassium, calcium, protein and glucose (Figs. 3-5). The occurrence of a circadian rhythm imputed for phosphate and sodium below the 10% level but was not found for creatinine and chloride ($p > .10$) in the blood of these patients. However, here as elsewhere ([1]), we must qualify the conditions of sampling and observation chosen for

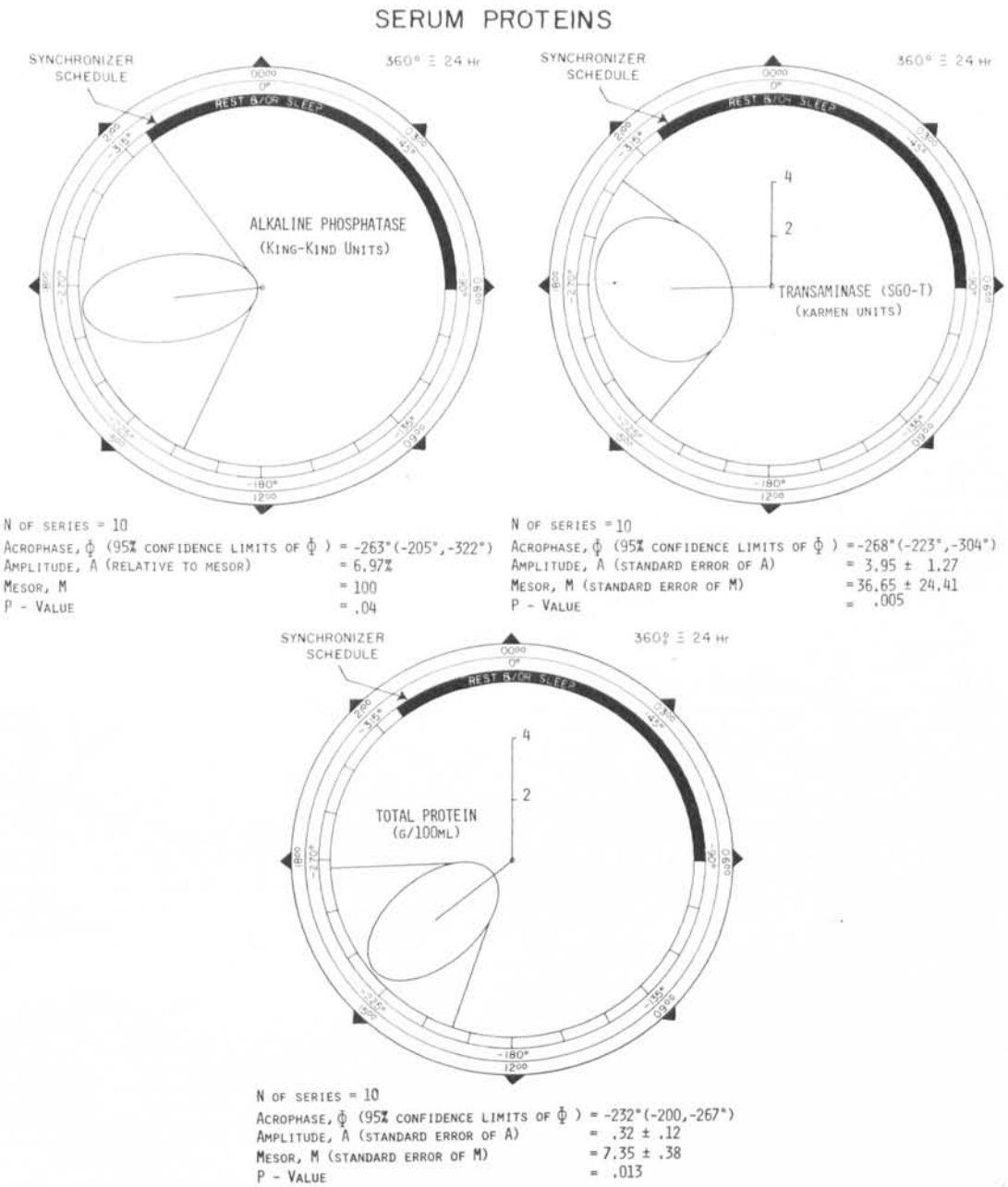

FIG. 4. Serum proteins.

this study as possibly underlying the failure to detect certain rhythms by cosinor. A bioperiodicity may well be detected on larger samples covering longer durations. Another point that must be further explored for all variables are any contributions of diet and recumbency versus orthostasis and activity. For glucose in particular, the variations here reported must be regarded as largely alimentary in timing and perhaps in origin as well.

The timing of those rhythms ascertained to be statistically significant indicated that a number of them were reasonably well locked into phase with one another: this becomes apparent from similar acrophases, e.g., for direct and total bilirubin with ϕ in the forenoon. The lack of overlap of the 95%

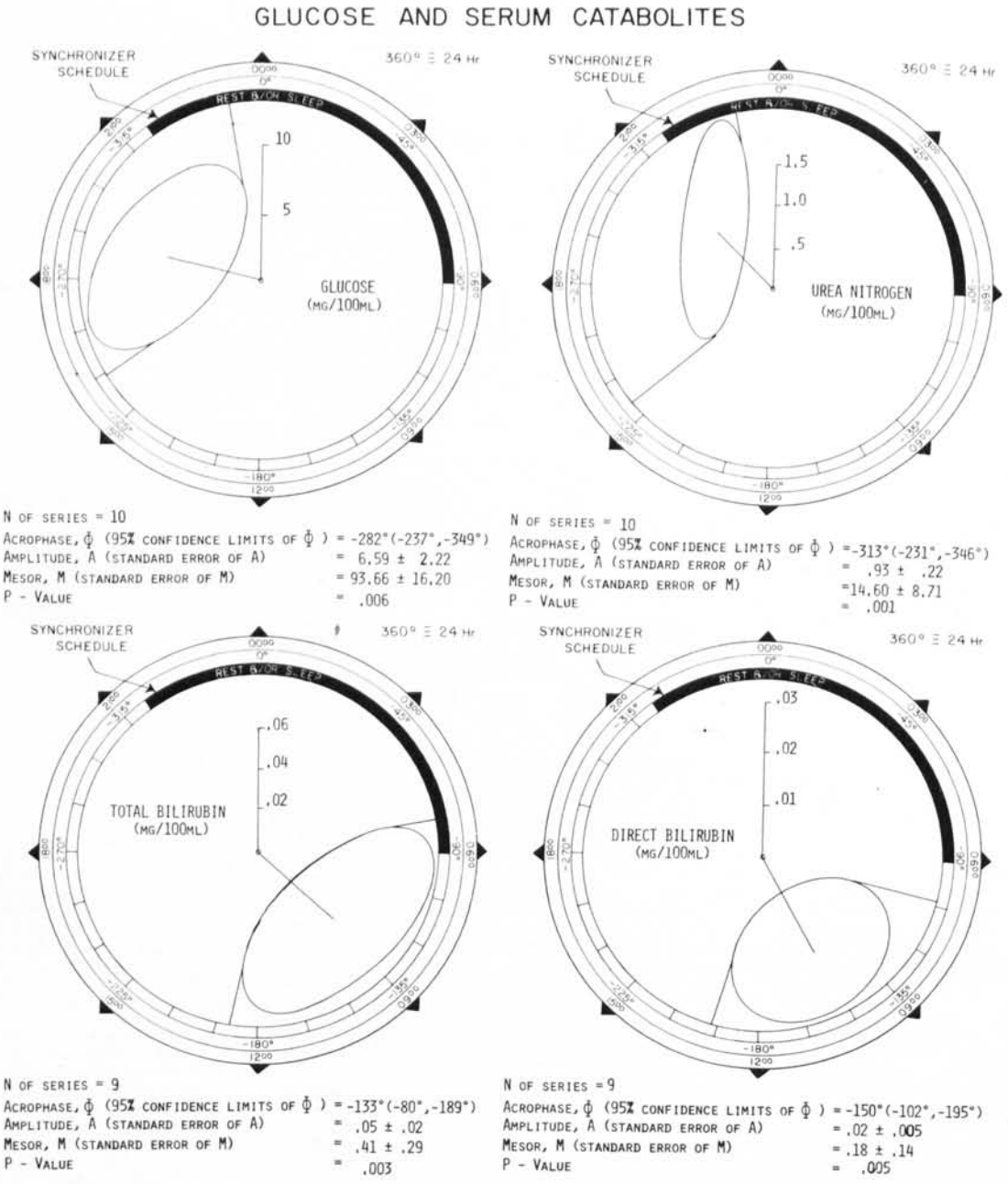

FIG. 5. Glucose and serum catabolites.

confidence arcs for the bilirubin ϕs on the one hand and for most other blood ϕs on the other hand can be seen by comparing the different cosinor plots. The SGOT rhythm showed a statistically significant difference in timing for these patients as compared to healthy subjects studied earlier [3, 4, 5]. Whether such a finding can be confirmed and, if so, whether it be due to the disease, to medication, or to other factors constitutes a problem awaiting further study.

Urine. Rhythm detection by cosinor was feasible for urine temperature and rates of excretion for volume, sodium, potassium, chloride, 17-ketogenic steroids, epinephrine and norephinephrine (Figs. 6, 7). In pH only did the cosinor method fail to ascertain sta-

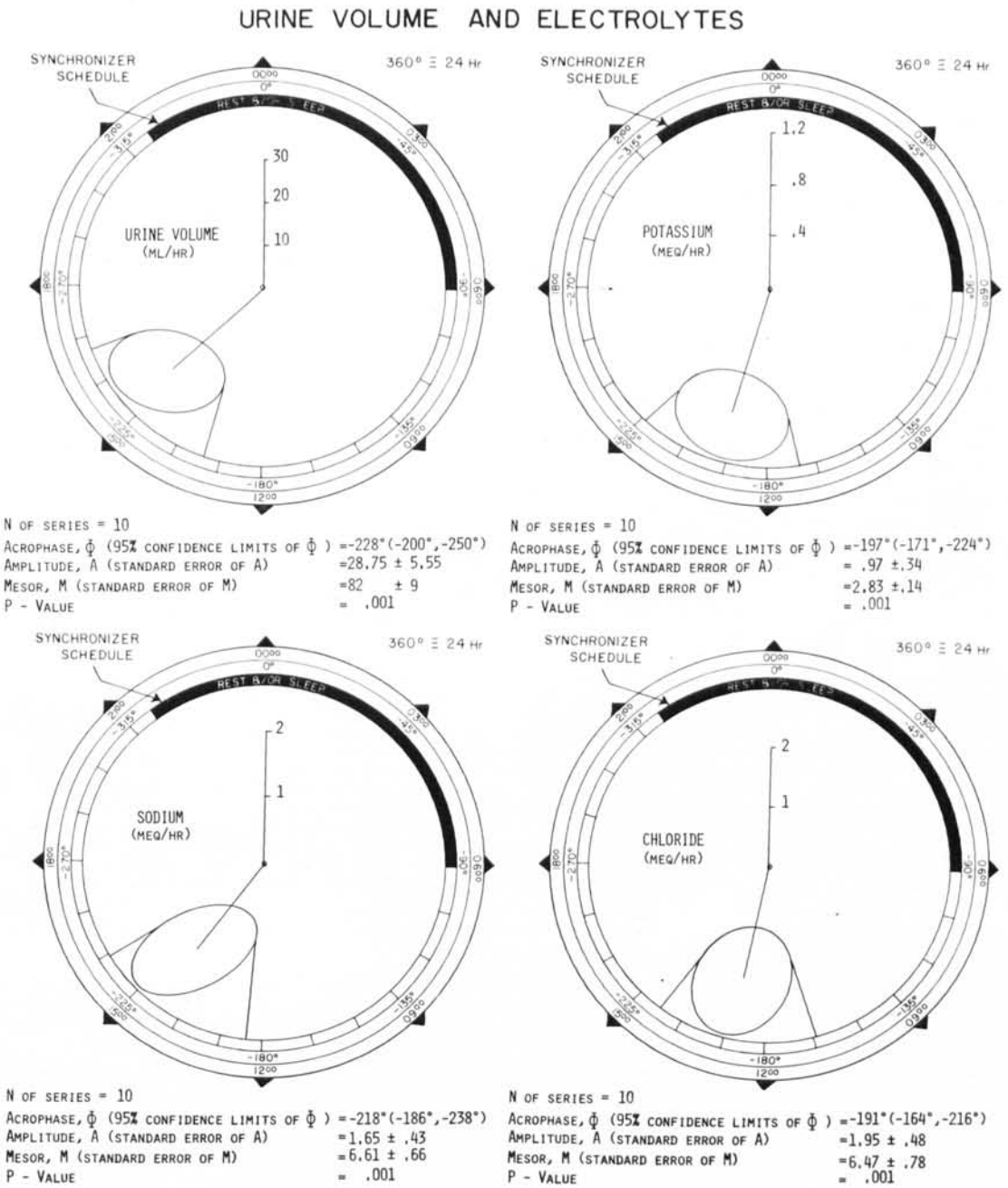

FIG. 6. Urine volume and electrolytes.

tistical significance for the occurrence of a circadian rhythm. The timing, amplitude and mesor of some of these prominent rhythms in urinary variables of patients with leprosy are shown in the figures.

DISCUSSION

This study was undertaken to determine whether leprosy is compatible with circadian rhythmicity. Added questions as to whether these rhythms and/or other features of an organism's spectral structure are altered in such patients await study.

Whether or not a spectral-structure alteration or chronopathology is demonstrable, it is desirable to be aware of the presence of rhythms and to consider the possibility that they may constitute a useful guide to be

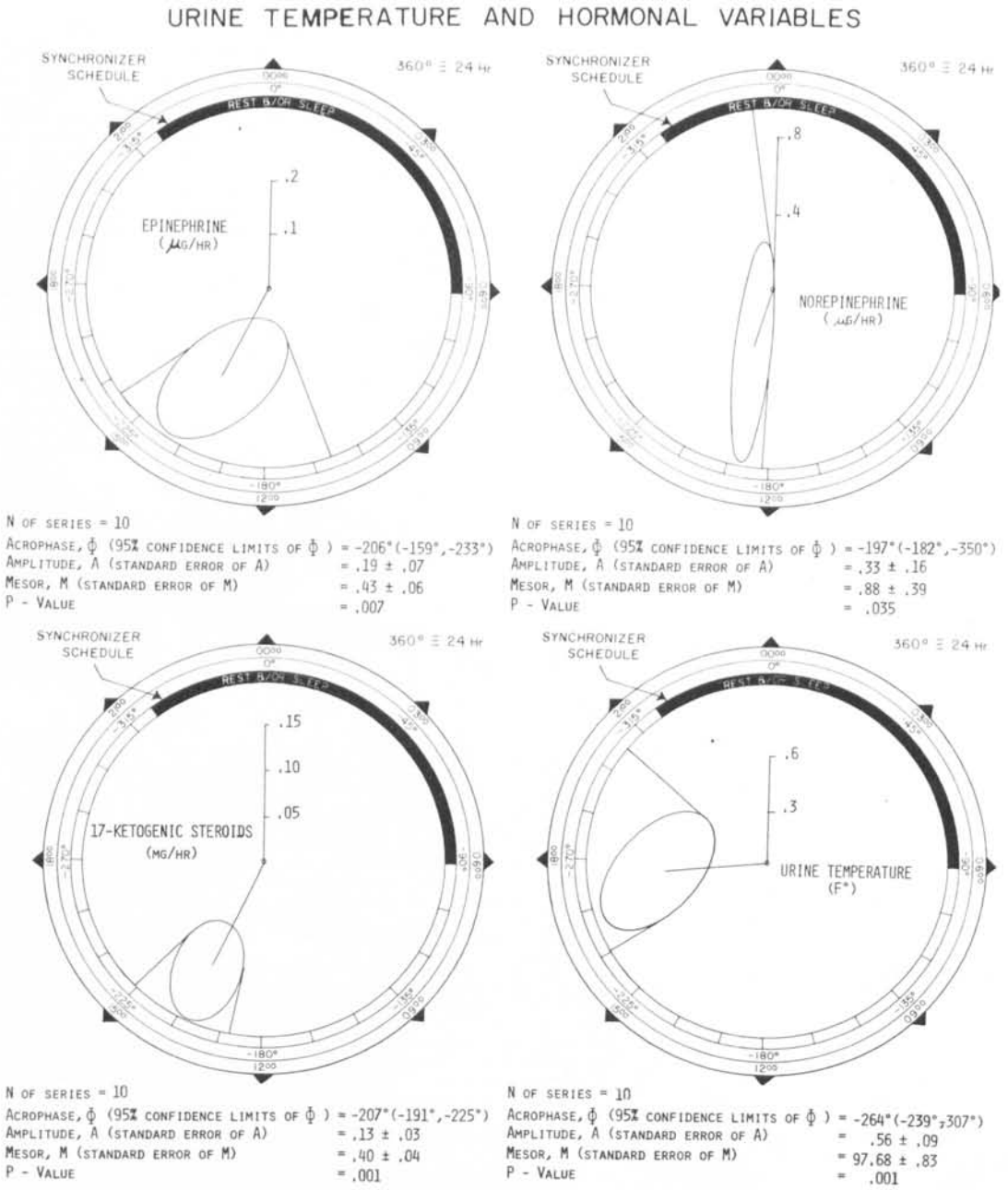

FIG. 7. Urine temperature and hormonal variables.

evaluated in timing therapy for the prevention of reaction. In order to approach such problems, it was necessary to obtain a data base for exploring the following questions:

a) Do patients with leprosy exhibit circadian rhythms in their vital signs as well as in behavioral functions and biochemical variables of blood and urine?

b) If so, what is the extent of change (or amplitude) of these rhythms and what is their timing (their so-called acrophase)?

Answers to these basic questions have been provided by this study. A rhythm has been demonstrated for a number of behavioral, biophysical and biochemical functions in patients with leprosy. The methods for resolving such a circadian time structure were applied to relatively short series of data

covering at most ten days. Because of this circumstance, rhythms with longer periods that may indeed characterize patients with leprosy remain beyond the scope of this presentation.

Moreover, sampling was restricted to the hours of wakefulness except for the study on blood which was carried out at 3 hour intervals for a full 24 hour span. Because of the 3 hour interval, certain ultradian rhythms with frequencies higher than one cycle in six hours [i.e., one cycle in twice the interval between consecutive samples (the Nyquist or folding frequency)] ([5]), are not readily amenable to analysis, and hence their discussion also remains beyond the scope of this study. For instance, any changes associated with REM sleep are here ignored.

A discussion of the waveform of rhythms in these patients against the background of the waveforms in controls will follow in another presentation. We may question whether a waveform may be well reproduced by sampling during the wakefulness span only and this too will be the subject of further study. It is pertinent, however, that for rhythm detection one can often restrict sampling to less than the entire 24 hour span; this is the more important since in many cases involving active participation by a subject (such as performance tests) one could not possibly sample without disturbing sleep and thus the very rhythms under study. One must compromise between not interfering with the subject and getting as many data as possible, to cover at least one full period of a rhythm investigated or preferably many such periods. For each study's particular aim, the corresponding minimal sampling requirements must be established initially from extensive data; but it has been shown that when data for intraperitoneal temperature, automatically recorded at ten minute intervals through telemetry, are analyzed and thereafter analyses are repeated after omitting every second datum, every second and third and so on, one still can with these relatively few data points not only detect a rhythm but also reproduce some features of the original curve.

Actually, with a view toward making the sampling of blood more generally practical in future studies, the blood data should further be analyzed to see how well the original curve can be reproduced after omitting the night portion. There is also the desideratum of "sampling when something happens," emphasized by O. H. Schmitt of the University of Minnesota (personal communication). In other words, it is important to sample at the time of a "spike" on a waveform resembling a sharp spike, simply because at other times one may not find any change. Thus the waveform and noise level largely determine whether or not measurements may be restricted to just a part of the rhythmic period under study; the more sinusoidal the waveform and the lower the noise, the more readily the rhythm's detection and quantification are feasible with small samples. Since some noise is always present, the cosinor presentation of the findings represents a useful transformation and summary of the data. Instead of a summary in rectangular coordinates, a polar display indicates not only a point estimate of acrophase (i.e., a given hour and minute for the timing of high values) along with some value for the average extent of change or amplitude, but also the 95% confidence intervals for both these characteristics, describing the extent of change and the timing.

SUMMARY

We have herewith examined the characteristics of circadian rhythms in patients with lepromatous leprosy, active or inactive, allowing a comparison with corresponding properties of rhythms in healthy subjects mapped earlier. Group results were illustrated by cosinor plots, produced directly on microfilm by computer. Eventually such reference standards in the form of cosinors, among other displays, notably of waveform, may be individualized and carried on a person's health record. Such a quantitative assessment of an individual's rhythms in health may serve for rigorous comparison with any changes accompanying increased susceptibility or occult or overt disease.

RESUMEN

Nosotros hemos examinado las caracteristicas de los ritmos circadianos en pacientes con lepra lepromatosa activa e inactiva, y las hemos comparado con las correspondientes propiedades de esos ritmos en sujetos normales. Los resultados grupales fueron ilustrados mediante diagramas consinor, producidos directamente en microfilm en la computadora. Eventualmente

tales standards de referencia en forma de cosinors, entre otros graficos, particularmente en forma de ondas, pueden ser individualizados e incorporados a la historia clinica. Estos registros cuantitativos de los ritmos de individuos normales pueden servir como base de rigurosa comparacion con cualquier otro cambio que acompane un aumento de la suceptibilidad o de enfermedad oculta o manifiesta.

RÉSUMÉ

Nous avons examiné les caractéristiques des rythmes circadiens chez des malades souffrant de lèpre lépromateuse active ou inactive, en vue de procéder à une comparaison avec les propriétés correspondantes de ces rythmes chez des sujets sains, telles qu'elles avaient éte reconnues auparavant. Les résultats groupés ont été reproduits de manière illustrative sur des graphiques cosinors tracés directement sur microfilm par un ordinateur. A l'occasion, des standards de références, sous la forme de cosinors, peuvent être isolés au même titre que d'autres reproductions graphiques telles que des tracés de fréquences, et reproduits dans le dossier médical d'un individu. L'évaluation quantitative des rythmes d'un individu peut être utilisée pour procéder à des comparaisons rigoureuses, par rapport à des modifications associées à une susceptibilité accrue à une maladie déclarée ou inapparente.

Acknowledgment. Invaluable help was provided by Walter Nelson, Administrative Scientist, and Robert Sothern, Junior Scientist, both of the Chronobiology Laboratory, University of Minnesota, Minneapolis, Minnesota in the editing of the manuscript and in numerical analyses, respectively.

APPENDIX

Brief summaries follow of patient disabilities and medications received during the ten day sampling span.

1810 R.H. Total loss of hearing of left ear. Claw deformities of ring and little fingers of both hands. Lower extremities amputated prior to study: right—above knee, 10 years 7 months before study; left—below knee, 6 years 3 months before study.

Medications: a), Diasone® 330 mg (oral) Monday through Thursday (1 tablet 4 × week) given at 08:00 on August 20, 21, 25, 26, 27 and 28; b) hexavitamins—one daily at 08:00.

2174 A.G. Left hand deformed with sensory perception impaired.

Medications: a) Colace 100 mg B.I.D. daily at 08:00 and 20:00; b) Diasone® 330 mg 3 × week, given at 08:00 on August 20, 22, 25, 27 and 29; c) Milk of magnesia 1 oz given at 20:30 on August 20 and 26. Note: surgery on this patient was done on August 21, 1969 at 13:30 on his insistence and as a desideratum for participation. A split-thickness skin graft was applied to an ulcer overlying the left heel. No pre-op medication was given.

2334 C.C. Superficially impaired sensory perception of both hands.

Medications: a) Diasone® 330 mg 6 × week given on August 20, 21, 22, 23, 25, 26, 27, 28 and 29 at 08:00; b) Phenobarbital, gr ½ – 3 × day at 08:00, 12:00, and 17:00; c) Pyridium 2 tablets 3 × day 08:00, 12:00, and 17:00; d) Placidyl 0.5 gm HS at 22:10 on August 27 only; e) Talwin 30 mg on August 21, 23, 25, 26, 28 and 29 at 22:00; f) Tetracycline 250 gm 4 × day, 08:00, 12:00, 16:00, and 20:00 on August 20 and 21; g) Darvon 65 mgm given on August 20 at 05:30, 14:00, and 21:45; on August 21 at 05:45 and 15:30; on August 24 at 04:00 and 20:00; on August 25 at 05:00, 14:00, and 18:00; on August 26 at 18:00; on August 27 at 05:00, 12:30, and 17:10; on August 28 at 07:00 and 15:20; and on August 29 at 05:30 and 13:10.

2453 A.C. Acutely active disease manifest mainly by numerous macular skin lesions, responding to therapy. No gross deformities or remarkably impaired sensory perception of the hands noted.

Medications: a) DDS 100 mg 3 × week, August 22, 27, 29 at 08:00; b) Indocin 25 mg. 4 × day, 08:00, 12:00, 17:00, and 20:00; c) Darvon 32 mg on August 20 at 23:30; on August 23 at 20:00; on August 24 at 20:00; and on August 26 at 20:00; (d) Phenobarbital 30 mg 4 × day on August 27, 28, and 29 at 08:00, 12:00, 17:00, and 20:00.

2684 N.L. Has had negative skin smears for only six months prior to sampling and was classified as active since inactivity in our definition entails zero BI for twelve consecutive months and this criteria is not met by this patient, and hence analyses were done by including and excluding him from the active group, but separate group analyses are not reported. Hearing of right ear impaired. Gross deformities or impaired sensory perception of hands not noted.

Medications: a) DDS 100 mg 3 × week given at 08:00 on August 20, 22, 25, 27, and 29; b) vitamin B 300 mcg 1M 2 × week given at 07:00 on August 22, 26, and 30.

2793 R.G. Bilateral impaired vision due to active corneal disease. Right visual field limited by recent tarsorrhaphy. Gross deformities or impaired sensory perception of the hands not noted.

Medications: a) DDS 100 mg 4 × week given on August 20, 21, 23, 25, 27, and 29; b) I.N.H. 100 mg 3 × day, given at 08:00, 12:00, and 17:00; c) Elavil 25 mg daily at 08:00; d) Darvon comp. 65 mg given August 29 at 18:45.

2885 J.A. One year and 11 days before start of sampling, a tendon was surgically transferred to

correct a deformity of left hand from paralysis of intrinsic muscles to thumb and fingers. Right hand shows clawing of the ring and little fingers and intrinsic weakness of the index and long fingers from complete ulnar and partial median nerve paralysis.

Medications: a) DDS 100 mg 4 × week at 08:00 given on August 20, 21, 25, and 28; b) Librium 10 mg 3 × day, daily at 08:00, 12:00, and 17:00; c) Probanthine 15 mg 3 × day, daily at 07:00, 11:00, and 16:00, also 30 mg HS daily at 20:00; d) Robaxin—started August 28—1 gm 4 × day, received medication on August 28 at 16:00 and 20:00 and on August 29 at 08:00, 12:00, 16:00, and 20:00; e) Maalox at bedside PRN; f) Scopolamine O.U., drops daily at 09:00.

2898 H.P. Six months before start of sampling, a tendon was surgically transferred to correct deformities of all fingers and thumb of left hand. Right hand—the ring and little fingers rigidly clawed.

Medications: a) DDS 100 mg 5 × week given at 08:00 on August 20, 21, 22, 25, 26, 27, 28, and 29.

2921 A.H. Moderately impaired hearing of right ear, bilateral lagophthalmos (inability to open and close eyelids), without eye disease sui generis, and bilateral manual deformities—clawing of all fingers and loss of intrinsic functions of both thumbs, with rigid flexion contractures of the interphalangeal joints.

Medications: a) DDS 100 mg on August 22, 25, and 29 at 08:00.

2926 J.G. Marked impairment of hearing of right ear, bilateral dropfoot deformity, and confinement to wheel chair.

Medications: a) DDS 100 mg 2 × a week, given at 08:00 on August 22, 25, and 29; b) Darvon comp. 65 mg given on August 20 at 18:45; c) Milk of magnesia 1 oz given at 20:00 on August 20, 23, 26, and 27.

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