TABLE I. Prevention of Ventricular Fibrillation with Quinidine during Profound Hypothermia.

Dog	Period of hypothermia	Low temp., °C	Cardiac arrest, min.	I.V. quinidine, mg/kg	V.F.
9	1	9	13	30	0
10	1	6	22	35	0
11	1	6.5	20	28	0
13	1	5	26	32	0
6	1	1	19	20(I.M.)	Rewarm
	2			25	0
7	1	8.8	9	30	0
	2	9	8		0
	3	8.2	7		0
	4	9	9		Rewarm
8	1	8.2	19	30	0
	2	8.8	13		0
	3	9.5	11	10	0
	4	10	10		0
18	1	7	60	30	0
21	1	7	74	30	0
22	1	7	68	30	0
23	1	7	69	30	0
24	1	7	74	30	0
26	1	7	60	30	0
27	1	5.5	65	30	0
28	1	6	68	30	0

V.F.—Ventricular fibrillation.

cant hypotensive effect of drug.

The mode of action of quinidine in prevention of ventricular fibrillation in profound hypothermia is not known. It is possible that suppressive action of quinidine may prevent premature firing of a stimulus or premature response to stimuli when there are still critical temperature gradients in heart that prevent uniform myocardial response(5).

Complete circulatory standstill for as long as one hour is tolerated at temperatures below 10°C. This with demonstration of simple method of preventing ventricular fibrillation suggests many possibilities for surgical applications of this technic.

Summary. In a series of animals with esophageal temperatures reduced to 10°C or lower by core cooling, ventricular fibrillation has been regularly prevented with intravenous infusion of quinidine.

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Exogenous Timing of Rat Spontaneous Activity Periods.*† (24979)

FRANK A. BROWN, JR. AND EMMA D. TERRACINI
Dept. of Biological Sciences, Northwestern University

While numerous investigations have resulted in descriptions of periodic patterns of spontaneous locomotor activity in mammals in constant conditions, particularly those with periods approximately 24-hours in length, very little progress has been achieved in resolving the mechanism by which these mammalian periodisms are timed. Brown, Shriner and Ralph(1), studying a male white rat, both in conditions of constant darkness and constant low illumination, found 24-hour cycles under the former conditions and 25¼-hour cycles under the latter. Utilizing the rat's 25¼-hour overt rhythm of running to randomize the overt running relative to time of solar day (24-hours) and lunar day (24.8-hours), these investigators found, underlying the overt 25¼-rhythm, both solar-day and lunar-day rhythmic components. The more conspicuous was lunar-day one, with rat running about 3 times as much at lunar nadir as at lunar zenith. It was postulated that these natural-period cycles constituted reference

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clocks for timing rat's overt running cycles. However, the highly dominant overt 25¼-hour activity pattern contributed such variance to data as to preclude proper quantitative analysis of any existing interrelationships among the various periodisms. The following study was carried out to determine reproducibility of earlier results, and to attempt to learn more concerning this very fundamental problem. In view of the special nature of the results obtained, it should be emphasized that this study does not involve a selected case; it is the first and only study of the rat carried out in our laboratory since the earlier reported one.

Methods. One adult male white rat was placed in a modified Hemmingson-Krarup activity recorder(2) on Jan. 11, 1959. The recorder was kept in photographic darkroom continuously illuminated dimly (ca. 10 lux) through voltage-regulated power supply. Temperature was thermostatically controlled at 24°C. The recorder was screened by black cloth from persons working irregularly, in the same room, and who, on 6 or 7 occasions during the study turned off the lights for 2 minutes to an hour. The running wheel activated, through micro-switch, a signal-magnet operated pen registering in another room, periods of wheel rotation. The rat had always available excess of food and water. Values indicating number of differentiable running periods for each hour of 60 consecutive days (Jan. 12 through Mar. 12, 1959) were obtained.

Results. Tabulation of results revealed a conspicuous overt, lunar-day rhythm of running, the major period of running occurring 50 minutes later each day to yield a clear monthly repetition of daily patterns of activity. Maximum activity occurred over noon hour during each period of full moon. The data for each calendar day were consequently arranged to give their proper relationship as hours of lunar-day, with 12th hour being that of lunar zenith and 24th hour that of lunar nadir. This Table forms Fig. 1. It is evident that rat's spontaneous running is high for whole 60-day period during hours the moon is below the horizon and low when it is above. A gradual drift of 12 minutes/day in either

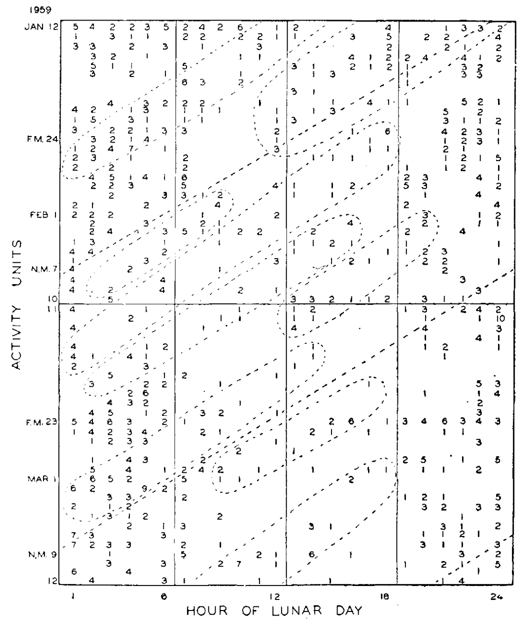

FIG. 1. Table including No. of activity periods of male white rat, kept in constant illumination and temperature, for each lunar-day hour during 60-day period.

direction away from precise lunar-day frequency would have resulted in period of activity moving completely from lunar "night" to lunar "day" over the 60-day period. Not only did such a phase drift not occur, but there is no suggestion of even such a slight phase drift over the lunar day as might indicate only a 2 or 3 minute a day deviation in the major rhythmic period from precise lunar-day frequency. These last deviations would have yielded a 2- or 3-hour phase shift, respectively.

Fig. 2, illustrating mean lunar-day cycles for each of 2 months (Jan. 12 to Feb. 10; Feb. 11 to Mar. 12), demonstrates reproducibility of these lunar-day cycles. The rat was more than 6 times as active at first lunar hour as at 11th one. The coefficient of correlation between comparable values for the 2 cycles was $+0.70 \pm 0.11$. The general similarity of the average of these 2 cycles with the average 58-day lunar-day cycle for period, Nov. 15, 1955 through Jan. 11, 1956 published earlier, for a different rat, is evident from the calculated correlation coefficient of $+0.56 \pm 0.14$ between corresponding lunar hourly values. Although an average solar-day cycle for

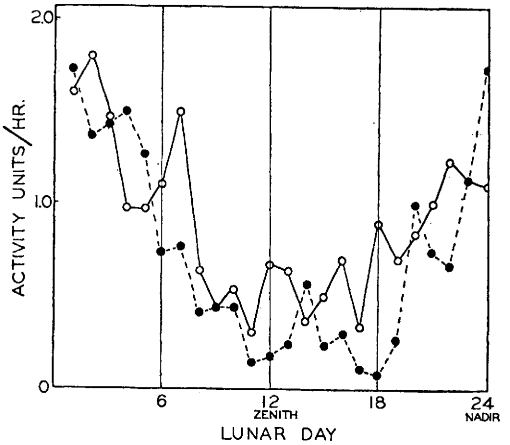

FIG. 2. Avg lunar-day cycle of running of the rat for 30-day period, Jan. 12 through Feb. 10 (solid line); for 30-day period, Feb. 11 through Mar. 12 (broken line).

the 60-day period was found with activity more than 50% higher at midnight than at 9 a.m., there was no significant correlation between corresponding hourly values of mean solar-daily cycles between first and second months. Hence, there was no sustained, reproducible fluctuation in activity of a solar-daily frequency comparable to that found for lunar day. The sharpness of lunar-day periodism of activity, however, enabled one to obtain some very suggestive information as to what underlies the failure to observe what might reasonably have been expected to be the predominant rhythmic period.

In Fig. 1 the broken diagonal straight lines indicate passage over lunar days of time of solar midnight. These lines, therefore, represent the slopes which would be paralleled by any patterns of locomotory activity possessing a solar-day frequency. A careful study of Fig. 1 reveals numerous clusters of data, especially evident during periods of relative inactivity in lunar day, which give indication of being of solar-day frequency. These either continue for a few days and terminate with no apparent explanation, or continue until engulfed in the overwhelming lunar-day periods of activity. It is possible that these transient solar-day periodisms, occurring at various hours of the day, were initiated by occasional times when food and water were replenished, or the weak illumination turned off, and that these transient daily cycles would not have become evident in wholly constant conditions. The 24-hour period itself was clearly not so imparted. Several of the more conspicuous of these solar-day recurring patterns are lightly outlined in the table.

Discussion. The foregoing results indicate the white rat possesses the capacity to display at the same time and same process rhythmic changes of 2 closely similar natural frequencies. These are the same periodisms which have been fully established as being derived continuously from external environment even in what physiologists have hitherto presumed constant conditions. The latter studies involved solar, lunar and annual rhythms of cellular oxidations(3,4,5,6).

Possession by the rat of a single autonomous periodism precisely the frequency of any single natural geophysical one is itself a highly improbable event; simultaneous presence of 2 autonomous periodisms both precisely those of major geophysical frequencies is even far less probable. Therefore, a reasonable hypothesis is that the 2 periodisms for spontaneous activity of the rat, differing in period by only 3½%, and exactly those of oxidative metabolism of numerous species of plants and animals, depend continuously upon force-fluctuations in the organism's environment effected by rotation of the earth relative to moon and sun.

Perhaps one of the most important suggestions from this study is that a behavior pattern, such as spontaneous locomotion, may be regulated through the same precise exogenous reference clock mechanism that is apparently responsible for regulation of periodisms in basal metabolic rate. This provides further evidence for a functional association between exogenous R oscillations and internal MI oscillations of the postulated(7) Responder-Mediator-Indicator mechanism of physiological-rhythm timing.

The results suggest that either of 2 exogenous metabolic periodisms, solar-day or lunar-day, depending upon other factors, is able to assume the dominant role in regulating the period of overt physiological cycles. This study, together with the foregoing one (1), also indicates that an overt cycle with period other than a natural one may or may not be present in the rat. In either case, however, the rat possesses the capacity for precise lunar-day and solar-day timing. Since the period of an overt rhythm which deviates from a natural one is known in the mammal (8) to be a function of constant illumination level, it is clear that such unnatural periods must be derived within the exogenously rhythmic organism in reaction with its environment. It has been pointed out(1,7) that all the evidence at hand is compatible with an hypothesis that the mechanism of their deviation involves the well-known phasing phenomenon, utilizing the demonstrated daily rhythm of sensitivity to light and temperature as phasing agents(9,10) to effect regular daily autophasing in constant conditions.

Summary. 1. A white rat displayed in constant low illumination a rhythm of spontaneous running of precise lunar-day frequency over 60-day study. This obviously resulted in accurate monthly recurrence of daily running patterns. 2. Activity was high during hours the moon was below the horizon, and low when above. Spontaneous running at first lunar hour was 6 times that at 11th hour. Correlation between average lunar-day cycles for 2 consecutive months was $+0.70 \pm 0.11$, and mean cycle for each month was quite similar to earlier published lunar-day cycle in the rat. 3. Superimposed upon the dominant lunar-day periodism were minor, transient, solar-day patterns of locomotor activity, terminating spontaneously or through apparent submergence in the larger amplitude, lunar-day cycles. 4. Since these 2 basic periodisms in rat activity, solar-day and lunar-day, are the same frequencies as the widely, and probably universally, distributed exogenous metabolic periodisms, they are considered simple behavioral expressions of a fundamental exogenous "clock-system" from which regular physiological rhythms of other than natural frequencies, often present, may be derived by the organism.

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Autoradiographic Studies of Antimitotic Action of Maleuric Acid.* (24980)

JESSE SISKEN, TADASHI A. OKADA AND EUGENE ROBERTS

Depts. of Biochemistry and Exp. Pathology, Medical Research Inst., City of Hope Medical Center, Duarte, Calif.

Maleuric acid (monomaleylurea) produces mitotic abnormalities and depresses mitotic index both in plant and animal cells(1).† In our study an analysis was made of mode of action of this compound on Ehrlich ascites tumor cells. By observing distribution of incorporated tritiated thymidine ($T\text{-}H^3$) in mitotic and interphasic cell populations using high resolution autoradiographic technics, it has been possible to show that administration of maleuric acid (MA) results in marked inhibition of the incorporation of $T\text{-}H^3$ into deoxyribonucleic acid (DNA) and, in addition, prevents progression of interphase cells into mitosis.

Methods. A sample of MA was obtained

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† LD_{50} in normal mice for single intraperitoneal injection was approximately 775 mg/kg and single daily doses of 150 mg/kg were tolerated for 8 days with no loss in weight or sign of toxicity.