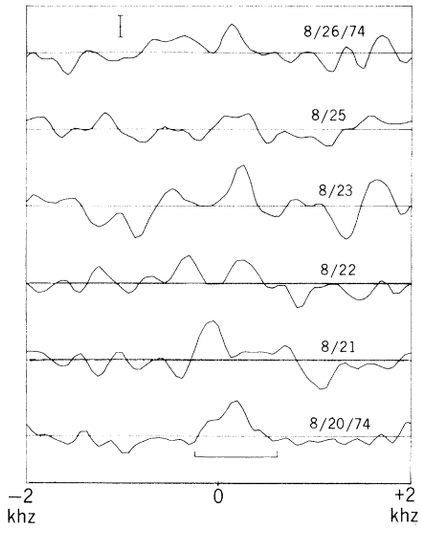

Fig. 2. Spectrograms measured from the Ganymede echo, each averaged over one night.

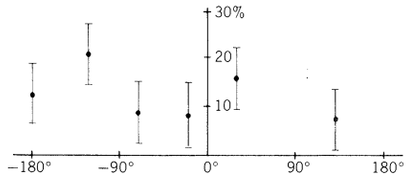

Fig. 3. Radar cross section of Ganymede as a function of phase angle (Jupiter-Ganymede-Earth). Error bars represent ± the formal standard deviation.

Table 1. Radar measurements at 12.6 cm.

Object	Radar cross section (%)	Roughness measure: half power angle (°)
Ganymede	12	21°
Mars	8	1° to 3°
Venus	12	4° to 6°
Mercury	6	7° to 8°
Toro	~8	~30°

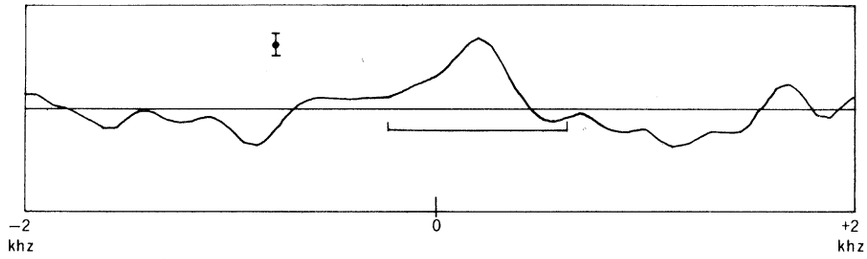

Fig. 4. Average of all the Ganymede spectra of Fig. 2.

which contains two kinds of information.

The first item of information is the total signal power, which corresponds to a radar cross section of 12 ± 2.5 percent. The second kind of information is the width of the spectrum. It corresponds to the power, reflected from an average surface element, which drops by half when tilted 21° from the line of sight. Because of this, the surface must have a considerable degree of roughness. The measured radar cross section is close to the value we have found for the terrestrial planets. The roughness of Ganymede, however, differs markedly from that of the terrestrial planets, being similar to our measurements of the small asteroid Toro. Table 1 summarizes these data.

What kinds of surface material have these qualities? Johnson and McCord (*3*), Pilcher *et al.* (*4*), and Fink *et al.* (*5*) have found strong evidence of water ice on the surface of Ganymede from their infrared spectra. Polarization studies by Veverka (*6*) show similar results. In addition, theoretical reasons have been advanced by Lewis (*7*) for expecting Ganymede to be composed largely of ice. A simple sphere of ice, however, does not fit well with the radar data. Such a sphere would have a radar cross section of less than 8 percent. If the surface were softened by an icy regolith or snow (which is likely for a planet of ice), then the radar cross section would be much smaller and the fit to the data would be worse.

Large, irregular blocks of ice could, by internal reflections, return more energy to Earth and thereby account for both the roughness and cross-section data. It is hard to find a mechanism whereby such blocks would be produced, however, and such a surface seems unlikely.

A second possibility might be a hard rocky surface similar to that of Mercury, but much rougher. Such rocks would have to be confined to the surface, since the density of Ganymede (2.0 g/cm^3) (*1*) is far too low for a rocky interior. Meteoritic influx could supply the material, but then one might expect the surface to be similar to that of Mercury, contrary to the data.

Perhaps the most likely possibility for the surface is rocky or metallic material embedded in a matrix of ice. Such a surface could be relatively smooth, with a top layer of ice rubble, but it could be rough to radar since the ice would be nearly transparent. As in the earlier case, the rocky material could result from meteoritic bombardment.

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21 October 1974; revised 14 February 1975

Chronotypic Action of Theophylline and of Pentobarbital as Circadian Zeitgebers in the Rat

Abstract. *In the rat the deep body temperature rhythm, monitored by telemetry, can be reset in a predictable direction by a stimulant (theophylline) and by a depressant (pentobarbital). When the drugs are applied immediately before or during the early active phases of the circadian cycle, the rhythm is set back (phase delay). When applied later, past the thermal peak, theophylline, but not pentobarbital, shifts the rhythm ahead (phase advance). Theophylline and pentobarbital in addition to having a number of already established pharmacological properties are now further identified as* chronobiotics: *they are drugs that may be used to alter the biological time structure by rephasing a circadian rhythm.*

It has been well established in a number of studies that a single stimulus delivered at the right time can advance or delay ("reset") the phase of a circadian oscillation (*1*, *2*). The relationship between the induced phase change and the circadian time of administration of the external stimulus has been called a phase response curve. In the

vast majority of such studies, light has been the zeitgeber [phase-resetter (*3*)] of choice. It is also well known that organisms are chronotypically sensitive (as measured by survival, trauma, or short-term physiological and behavioral sequelae) to a number of physical and chemical agents, including drugs used in clinical chemotherapy (*4, 5*). However, to date few pharmacologically oriented circadian studies have employed phase shift as an end point (*6*) or concentrated upon the use of a drug as a zeitgeber for the whole organism (*7*).

In yet another category, there is ample evidence to show that diverse circadian oscillations of intact vertebrates, whether in small experimental mammals (*4, 8, 9*), in birds (*2, 10*), or in man (*4, 9, 11*), are like sluggish timepieces, that may take days or a week or more to reset completely. It occurred to us that one could reduce this transit time [or "shift-time" (*4*)] by a proper prescription of multiple zeitgebers, and that this would then have practical impact in ameliorating not only time zone fatigue and the transient chronotypic ennui that classically follows circadian phase shift, but also problems in circadian dysphasia that may arise from the temporally improper administration of drugs as well. The zeitgebers of choice would have to be convenient, safe, and cheap, and would include the widely used *light* in light-dark (LD) cycles, and *food* in feed-"starve" (FS) cycles, but both of these would be supplemented by drugs already known for their effects upon sleep and wakefulness. Focusing upon the latter problem of drugs of choice, we narrowed the initial range to theophylline and pentobarbital, each being distinctive in action either as a stimulant or a depressant, yet each is "mild" enough to be commonplace in the medical pharmacopoeia or in dietary regimens, and is known to induce enzymes along key regulatory pathways of intermediary metabolism (*12*), theophylline being strongly chronotypic in its inductive efficacy (*13*), and pentobarbital showing a chronotypic soporific effect (*14*).

Eighteen rats (Sprague-Dawley) were housed singly in separate cages in two rooms of the Biotron controlled environment facility at Madison, Wisconsin, and their body temperatures were monitored over a span of 25 weeks following the intraperitoneal implantation of temperature telemeters. During the days preceding injection of a drug, the animals were routinely entrained by seven or more daily cycles of programmed feeding (FS) and illumination (DL), with food presented for only 7 hours of the day (FS 7 : 17) during the "dim" phase of a DL 17 : 7 cycle ($D \sim 50$ lux, $L \sim 800$ lux at cage level from 500-watt incandescent lamps); water was continually available. Entrainment was followed by a free-run interval (SSDD) during the first or second day of which subcutaneous injections of theophylline, pentobarbital, or saline were administered at prescribed intervals. Free run then continued for five or six more days under uniform environmental conditions (20°C, 50 percent relative humidity, in rooms isolated from sound and vibration, and with no room entry permitted). At the time of injection, the animals were between 19 and 30 weeks of age in the experiments described herein.

Temperatures were measured and recorded automatically at 15-minute intervals by a data acquisition system described elsewhere (*15*). Although the data points from hour to hour occupy an apparent error range of a degree or more in amplitude, the longitudinal macroscopic projections of all the data clearly show daily and circadian oscillations. Moreover the "error range" arises not from imprecision in telemetry, but from ultradian thermal episodes (*9*) of 10 to 34 minutes duration (*16*); the latter episodes are quenched by a sharp plunge in body temperature for an hour or more following theophylline or pentobarbital injections, and the thermal boundaries of these hypothermic wedges (Fig. 1) are clearly defined by straight lines connecting the data points, with a precision of about 0.01°C at each point. During entrainment, the daily rhythm in intraperitoneal temperature ranges from 36° to 39°C, with a peak occurring in the middle of D about 4 to 5 hours after feeding begins. Circadian oscillations continue during free run over a range of about 3°C; however, during prolonged SS (Fig. 1) a hypothermic drift is seen, and the average temperature can drop by as much as 0.3°C per day.

The digitalized thermistor frequencies were transformed by a second degree poly-

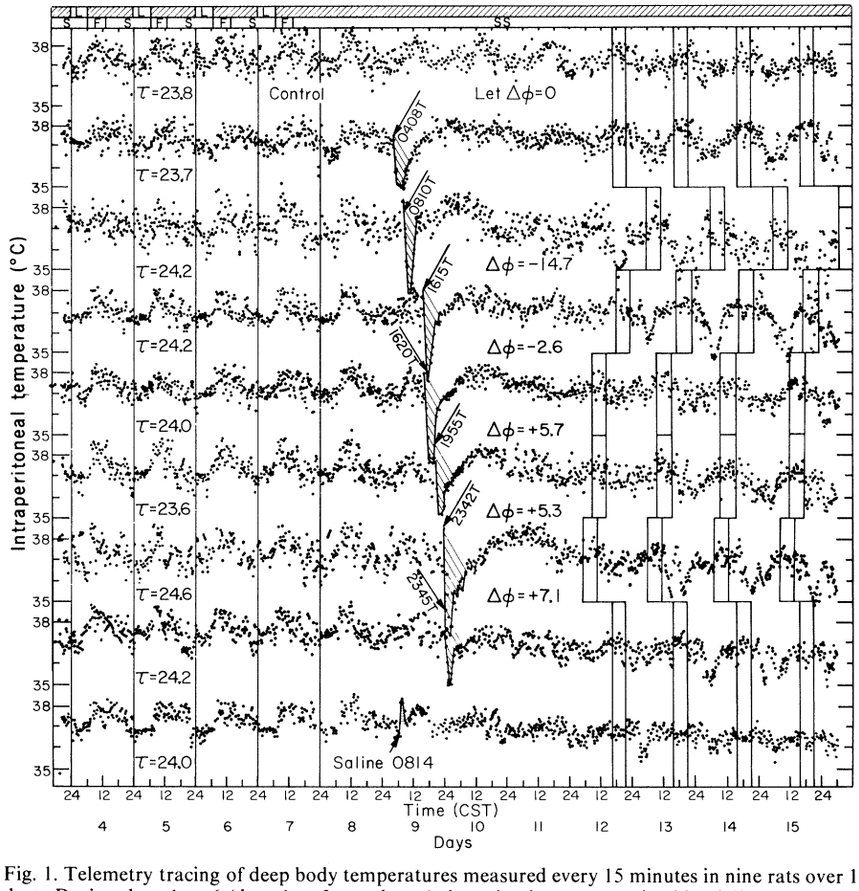

Fig. 1. Telemetry tracing of deep body temperatures measured every 15 minutes in nine rats over 12 days. During days 1 to 6 (days 1 to 3 not shown) the animals were entrained by daily programs of feeding (FS 7 : 17) and illumination (DL 17 : 7). The period (τ) was determined by power spectral analysis and autocovariance for the 4 days shown, and its limit approaches 24.0 hours as the number of days of entrainment becomes very large. During days 7 to 15 the rats "free ran" in constant dim light (DD) and without food (SS, top bars). Theophylline was injected (7.5 mg/100 g) at times shown by arrows on days 9 and 10. The rat at the top was uninjected; the rat at the bottom received saline only (at 0814 hours). The induced phase shifts ($\Delta\phi$), determined by the ratio of the cospectrum to the quadrature spectrum evaluated at a frequency of 1 cycle per 24.0 hours, are clearly chronotypic and are graphically highlighted by bars drawn through the thermal peaks on days 12 to 15.

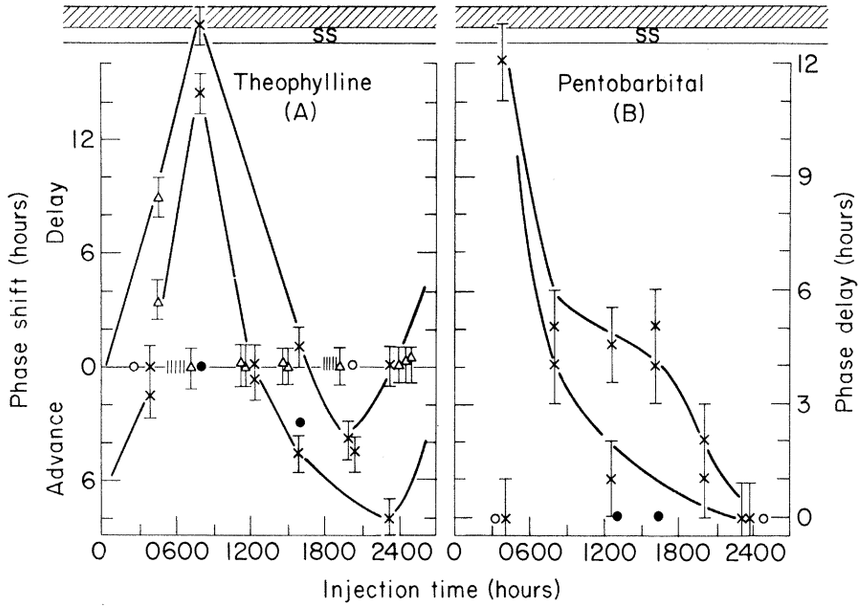

Fig. 2. (A) Phase response curve, relating magnitude and direction of theophylline-induced phase shift in thermal peaks of the rat, to the time of injection of the drug (crosses and triangles, 75 mg/kg). The results from three separate experiments are shown. In the first, injections were made on the second day of SSDD and the crosses and circles are data from the experiment shown in part in Fig. 1; the vertical brackets are the ranges of ± 1 hour for thermal peaks on days 13 to 15. Open and closed circles represent uninjected and saline-injected controls in that experiment; the phase advance of 3 hours at 1630 (closed circle) was the largest phase shift seen in any animal injected either with saline or with lower dosages of theophylline (see below) during the 6-month study. Triangles are data from a similar experiment at the same dosage of theophylline. The short vertical bars are from a third experiment at a lower dosage (30 mg/kg) in which, in ten rats, no phase shifts were induced. (B) As above, but for pentobarbital at 40 mg/kg, injected on the first day of free run.

nomial to the equivalent temperatures accurate to within 0.01°C. In a statistical analysis of the data given in Fig. 1 each animal's temperature record was divided into two time series, one consisting of the time before the onset of starvation and subsequent injection and one consisting of the time following the injection. Because of the obvious periodicity, and the lack of any apparent damping of the oscillations, these time series could be treated as stationary stochastic processes with Gaussian distributions (*17*). Autocovariance and power spectral estimates were computed for each series, as well as the cross covariance, cross spectra, quadrature spectra, and phase shift (as a function of frequency) between series (*18*). Although many methods are available for time series analysis (*19*), the above methods were selected because of their minimal restriction upon conformity of the data to a biased model. The development of a mathematical model based upon deep body temperature data already collected from animals subjected to a variety of LD, FS, and SS protocols is presently under way (*16*).

Figure 1 shows that theophylline (7.5 mg per 100 g of body weight) given at 0408 hours or at 2345 hours following a day and a half of SS had no lasting effect (days 12 to 15) in resetting the phase of the circadian clock in those rats. Rats injected at 1620 hours and at 1955 hours showed phase advances of 5.79 ± 0.75 hours and 5.30 ± 0.75 hours, respectively, and at 2342 hours an advance of 7.11 ± 0.75 hours; rats injected at 0810 and 0813 hours (the latter is represented only in Fig. 2A) showed phase delays of 14.74 ± 0.75 hours and 18 hours, respectively. Rats injected at 0408 and 2345 hours were not significantly different in phase from either the uninjected or saline-injected controls in this or any of the other series. The phase vectors as presented in Fig. 1 have been compared against the average displacement of the controls due to the transition from entrainment to free run (*16*). The complete results of this experiment (x's) and of two others like it are summarized in Fig. 2A as a phase response curve, which relates the phase vector (direction and magnitude) of the shift in thermal peaks to the time of application of the zeitgeber. The dramatic differences between animals injected at 2342 and 2345 hours are clearly not assignable to the 3-minute difference in injection times for essential replicas, but to the precipitous "cliff-hanging" discontinuity of the phase response curve at that phase of the circadian cycle (*20*).

It should be noted that at the lowest dose of theophylline administered (3 mg/100 g, ten rats, short vertical bars in Fig. 2A) and in saline-injected controls (closed circles) little or no phase shift was observed regardless of the time of injection. At a higher dosage (7.5 mg/100 g, 23 rats, x's and triangles) chronotypic phase shifts were induced, and the magnitude of the phase delay (during injection times from 0500 to 0900 hours) greatly exceeded the magnitude of the phase advance resulting from injections given from 1600 to 2400 hours. This result with *Rattus* is remarkably like that earlier reported for the flying squirrel *Glaucomys* by de Coursey (*21*) and interpreted by Pittendrigh (*20*) as "precisely what is demanded for good phase control" in a nocturnal species, except that in our case the zeitgeber is not light, but theophylline.

Not unlike light and the stimulant theophylline, the depressant pentobarbital can cause a dramatic phase shift, especially when given in the hours preceding or during the early active (rising body temperature) phase of the circadian cycle. As shown in Fig. 2B, an injection of pentobarbital (4 mg/100 g) given at 0419 hours or at 2335 hours on the first day of free run may have no effect on circadian phase measured in DDSS 5 or 6 days later (day 12 or 13 after start of entrainment). On the other hand, when pentobarbital was given during the active phase a significant delay was seen in five out of six cases; and at 0408 hours, immediately before the early active phase, the greatest phase delay (~12 hours) occurred at about the same time that none occurred in another rat given the same dose. It is clear that pentobarbital can be a very strong zeitgeber, and that the phase delays induced are compatible chronotypically with the phase response curves for theophylline (Fig. 2A) and for light in other nocturnal mammals (*1, 2, 20–22*).

In conclusion, we propose the feasibility in the near future of writing rational circadian phase control prescriptions for the transmeridianal traveler or shift-worker as he changes his work shift through some large phase angle of the circadian cycle. Winfree has already suggested, and we concur, that phase response curves such as seen in Fig. 2 (or "helicoids" in their most general form) "may provide a fundamental principle for dosage scheduling . . . when a 'pill' is discovered which rephases the circadian clock" (*23*). We also reckon that the effort required to extrapolate the results of pilot studies such as this one to man will be considerable, and will involve further screening of pharmacologically suitable zeitgebers as chronobiotics (*24*) in protocols employing multiple zeitgebers; preliminary results with theophylline have already shown that its chronotypic action can be applied to enhance phase delays in the rat even in the presence of food and

light cycling (*16*). In noting the efficacy of pentobarbital as a circadian zeitgeber, we cannot overlook the fact that low levels of phenobarbital in the diet are cocarcinogenic (*25*) or the possibility that the act of resetting a circadian oscillation by means of chronobiotic drugs or otherwise inevitably implies molecular-genetic manipulation (*26*) with attendant mutagenic and carcinogenic sequelae (*27*).

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27. Work in progress has shown that rats fed phenobarbital in the diet at dose levels that are cocarcinogenic have exhibited patterns of temperature control that are more dysphasic than circadian [see C. F. Ehret, V. R. Potter, A. McQueen, *Argonne National Laboratory Report 8070* (1973), p. 160]. Evidence relating to the deleterious action of aperiodic environments and loss of internal temporal organization has been cogently reviewed by C. S. Pittendrigh and D. H. Minis [*Proc. Natl. Acad. Sci. U.S.A.* **69**, 1537 (1972)].
28. This research was conducted in large part at the University of Wisconsin, Madison, Biotron, a controlled-environment research facility supported by the National Science Foundation and the University of Wisconsin. We thank the Biotron staff, especially L. Anderson and W. Handel for assistance in instrument maintenance and animal care at Madison; W. Eisler and J. Blomquist for help in data acquisition, programming, and processing at Argonne; M. Lichtenstein, P. Grothus, H. Burke, N. Linden, and J. Robinson for their help in animal and data handling; and Drs. C. Peraino and A. Winfree for helpful suggestions. The work was supported in part by the AEC and by the Research Committee of the Graduate School, University of Wisconsin, Madison.

24 January 1975

Flavonoids as Inhibitors of Lens Aldose Reductase

Abstract. *Flavonoids are effective inhibitors of lens aldose reductase. Quercetin, quercitrin, and myricitrin are significantly more potent than the previously known aldose reductase inhibitors. The inhibitory activity is of the noncompetitive type. In addition, quercitrin effectively blocks polyol accumulation in intact rat lenses incubated in medium containing high concentration of sugars.*

Although the ubiquitous distribution of flavonoids in the plant kingdom has been known for a long time, a biological action of this group of compounds in animals and man was first suggested by Szent-Györgi and his colleagues (*1*) who reported that flavonoids have the useful property of preventing capillary bleeding and fragility in scorbutic animals. Despite extensive studies in the 1950's (*2*), unequivocal proof for such a role on capillary permeability was not obtained; consequently interest in flavonoids waned (*3*). The question of their biological action, therefore, remains unanswered.

In the present report evidence is presented to show that flavonoids can exert an entirely different kind of biological effect—inhibiting aldose reductase. This enzyme has been involved in the formation of cataracts in diabetes and galactosemia (*4, 5*). The formation of sugar alcohols from sugars catalyzed by aldose reductase appears to initiate the cataractous process (*5*); inhibitors of aldose reductase are effective in delaying the onset of sugar cataracts (*5–7*). Further interest in aldose reductase and its inhibitors stems from the possibility that the enzyme may also be involved in the manifestation of some other secondary diabetic complications, such as neuropathy and angiopathy (*8*). The basis of this study was the possibility that flavonoids may be more effective than other known inhibitors of aldose reductase.

The inhibitory action of various flavo-

Table 1. Inhibition of lens aldose reductase by various compounds. The numbers indicate percentage of inhibition of the aldose reductase activity as compared to controls when the reaction was carried out in the absence of inhibitors. The number of experiments in each case was at least four. The standard deviation of the results was within 5 percent. All the compounds tested inhibited the enzyme activity almost completely at $10^{-4}M$. Abbreviations: TMG, tetramethylene glutaric acid; AY-22,284, 1,2-dioxo-1H-benz-(de)-isoquinoline-2(3H) acetic acid.

Inhibitors	Percentage of inhibition at the following concentrations		
	$10^{-5}M$	$10^{-6}M$	$10^{-7}M$
TMG	82	35	0
AY-22,284	90	40	0
Quercetin	83	60	15
Rutin	95	20	10
Quercitrin	95	88	55
Myricitrin	100	75	35
Morin	75	0	0
Hesperetin	50	0	0
2-Carbethoxy-5,7-dihydroxy-4′-methoxy-isoflavone	77	0	0
Robinin	56	0	0