Fever and motor activity in rats following day and night injections of *Staphylococcus aureus* cell walls

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Received 3 November 1999; accepted in final form 8 March 2000

Luker, Frank I., Duncan Mitchell, and Helen P. Laburn. Fever and motor activity in rats following day and night injections of *Staphylococcus aureus* cell walls. *Am J Physiol Regulatory Integrative Comp Physiol* 279: R610–R616, 2000.—Body temperature and physical activity are affected by both circadian cycles and pyrogens. We injected intraperitoneally 2.5 × 10⁹ cell walls of the gram-positive organism *Staphylococcus aureus* or sterile saline at three different times in the circadian temperature and activity rhythm of Sprague-Dawley rats. Irrespective of whether pyrogen injections were made when the rats were inactive (injection at 0900), just before the nighttime rise in activity and body temperature (1630), or during high activity (2100), the peak body temperature attained and the time to reach peak temperature were indistinguishable. The fever response, as measured by the thermal-response index, was greatest, however, when body temperature and activity were in the lowest phase. Physical activity was inhibited by night but not day injection of *S. aureus*. Our results provide the first description of experimental fever resulting from a gram-positive pyrogen in rats and the first time an aspect of sickness behavior (suppressed motor activity) has been associated with fever resulting from simulated gram-positive bacterial infection.

Physical activity; circadian rhythms; gram-positive bacteria

**METHODS**

Rats (4, 14, 19) and other rodents (17) have wide circadian temperature variations such that average body temperature during the daylight hours is ~1°C lower than it is at night. This difference approximates the extent of the rise in body temperature, which can be induced experimentally by injection of a pyrogen in this species, so that a diurnal fever may appear simply as an attenuation of the circadian rhythm. Rats also show strong circadian variations in physical activity (30), being much more active at night. Recently, interest has grown in the sickness behaviors that accompany pyrogen injection, of which suppression of physical activity is one aspect (11). We sought to find out not only how the body temperature response to pyrogen injection would vary at different times in the temperature cycle, but whether physical activity too would be affected differently by injections of pyrogen at different times of the activity cycle. To do so, we induced fever at three times of the circadian temperature and activity cycle of rats: when temperature and activity were low, just before the onset of the nocturnal increase in both temperature and activity, and during the plateau of highest body temperature and activity.

We used as a pyrogen a single dose of the cell walls of the killed gram-positive bacterium *Staphylococcus aureus*, and, to our knowledge, ours is the first description of the experimental use of a gram-positive organism for fever induction in rats and the first test of its ability to induce any aspects of sickness behavior in any species. Evidence already exists that gram-positive bacteria are pyrogenic in rabbits (7, 31) and sheep (9), and intravenous injection of their cell walls produces a biphasic thermal response similar to that produced by gram-negative lipopolysaccharide (LPS) injection, except for a longer latent period.

**Animals.** We used 10 female Sprague-Dawley rats, each housed individually, at a controlled ambient temperature of 24°C, with a 12:12-h light-dark cycle (lights on at 0600). Experimental interventions were carried out with the rats remaining in their home cages. Body mass of the rats at the commencement of the study was 201 ± 8 g (mean ± SD). Rat
chow (Epol, Johannesburg, South Africa) and water were provided ad libitum. All procedures were cleared by the Animal Ethics Committee of the University of the Witwatersrand, under protocol 96/40/4.

We included in our analysis the data from rats from which we obtained a complete data set for both pyrogen and control injections for a particular intervention. That reduced our group size to five in some cases. However, the narrow error bands we obtained (see, for example, Table 1) led us to believe that the results would have been the same if we had added more animals; so it would not have been ethically justified to do so.

**Temperature measurements.** We measured core body temperature of the rats using temperature-sensitive radiotelemeters (MiniMitter, Sunriver, OR). Each telemeter weighed 3–4 g when waxed (Elvax, MiniMitter). We calibrated the telemeters in a water bath at different ambient temperatures against a precision thermometer (Quat 200, Heraeus); their calibrated accuracy was between 0.05 and 0.1°C.

We implanted a sterilized telemeter into the abdominal cavity of each rat during a short sterile surgical procedure with the rats under ketamine (0.8 ml/kg) and xylazine (0.2 ml/kg) anesthesia. The rats were allowed at least 1 wk to recover from surgery before experimentation. The output from the telemeters (frequency in Hz) was monitored by a receiver plate (RTA-500) placed under each rat’s cage and fed into a peripheral processor (Datacol-3 Automated Data-Acquisition System, MiniMitter) connected to a personal computer. We recorded body temperature every 10 min over the day before, the day of, and the day after each experimental intervention.

**Activity measurements.** The data-acquisition system also allowed us to make continuous measurements of activity of the rats based on detection of telemeter movement. The receiver plate was larger than the floor of the rat’s cage. Activity counts accumulated over a 10-min period, coinciding with the time of temperature readings.

**Preparation of pyrogen.** We obtained commercially available cell walls of the gram-positive bacterium *Staphylococcus aureus* (Pansorbin cells) from Calbiochem. The cells were heat-killed and Formalin-fixed and supplied as a suspension in phosphate-buffered saline. We determined, using a hemocytometer, the concentration of the cells in suspension to be 1010 cells/ml and made dilutions in sterile saline to the desired pyrogenic dose. The pyrogenicity of the suspension was confirmed by intravenous injection of rabbits (results not shown).

**Experimental procedure.** We administered a dose of 2.5 × 10⁸ S. aureus cell walls suspended in 0.5 ml of sterile saline intraperitoneally to rats at 0900 (n = 5), 1630 (n = 8), and at 2100 (n = 8). Each rat served as its own control by receiving 0.5 ml of sterile saline instead of the S. aureus, at each of the three different times. The rats were hand-held for purposes of making the injections. We allowed a minimum of 3 days to elapse between saline injections and a minimum of 6 days to elapse between pyrogen injections. Times of injections and order of saline and pyrogen injection were randomized.

**Statistical analysis.** We calculated differences in the responses of each rat to *S. aureus* and saline injections by calculating areas between the curves of temperature versus time to obtain differential temperature response indexes (DTRI, °C · h) and between the curves of activity versus time to obtain differential activity response indexes (DARI, counts · h). Statistical analyses were performed using ANOVA, Student’s paired or unpaired t-test, and the Student-Newman-Keuls test for multiple comparisons post hoc. We considered values of P ≤ 0.05 to be statistically significant, and our results, unless otherwise stated, are expressed as mean values for the group of rats ± SE.

**RESULTS**

**Body temperature responses.** A summary of body temperatures before injection as well as the body temperatures during the day and night following injection of saline or *S. aureus* is found in Table 1. Although body temperature apparently was higher for the injections at 2100, there were no significant differences (P > 0.05, Student-Newman-Keuls) in the preinjection body temperatures at 0900, 1630, and 2100 before injection of saline or *S. aureus*.

Mean daytime body temperature was significantly different from mean nighttime body temperature for all interventions except *S. aureus* injection at 0900. This finding is consistent with the strong circadian rise in body temperature of rats during nighttime. When *S. aureus* was injected at 0900, a rise in body temperature occurred during the day such that the difference in average body temperatures between day and night was eliminated.

Table 1. Thermal and activity characteristics of rats given intraperitoneal saline or 2.5 × 10⁸ S. aureus cell walls at 0900, 1630, or 2100

<table>
<thead>
<tr>
<th>Time Of Injection</th>
<th>0900</th>
<th>1630</th>
<th>2100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saline</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection, °C</td>
<td>37.4 ± 0.3</td>
<td>37.3 ± 0.2</td>
<td>37.8 ± 0.2</td>
</tr>
<tr>
<td>Average daytime, °C</td>
<td>37.5 ± 0.1</td>
<td>37.2 ± 0.1</td>
<td>37.1 ± 0.1</td>
</tr>
<tr>
<td>Average nighttime, °C</td>
<td>38.1 ± 0.1</td>
<td>37.9 ± 0.1</td>
<td>37.8 ± 0.1</td>
</tr>
<tr>
<td><strong>S. aureus</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Preinjection, °C</td>
<td>37.4 ± 0.3</td>
<td>37.4 ± 0.2</td>
<td>37.6 ± 0.2</td>
</tr>
<tr>
<td>Average daytime, °C</td>
<td>38.2 ± 0.2*</td>
<td>37.3 ± 0.1*</td>
<td>37.1 ± 0.1</td>
</tr>
<tr>
<td>Average nighttime, °C</td>
<td>38.1 ± 0.1</td>
<td>38.3 ± 0.1*</td>
<td>38.1 ± 0.1*</td>
</tr>
<tr>
<td><strong>Peak, °C</strong></td>
<td>39.1 ± 0.3</td>
<td>39.0 ± 0.2</td>
<td>39.0 ± 0.2</td>
</tr>
<tr>
<td>Maximum change, °C</td>
<td>1.7 ± 0.3</td>
<td>1.8 ± 0.2</td>
<td>1.4 ± 0.1</td>
</tr>
<tr>
<td>Latency to onset, min</td>
<td>102 ± 9</td>
<td>91 ± 7</td>
<td>110 ± 4</td>
</tr>
<tr>
<td>Latency to maximum, min</td>
<td>230 ± 26</td>
<td>201 ± 18</td>
<td>195 ± 14</td>
</tr>
</tbody>
</table>

Values are means ± SE; n, no. of rats. Daytime, 0600–1800; Peak, highest temperature reached. Maximum change is from preinjection body temperature to peak. *Significant differences between saline and *S. aureus* administration (P < 0.01, paired t-test). †Significantly different from value for 2100 injection (P < 0.05, t-test).
In these instances, the fever appeared to have subsided before the decline in body temperature, which occurred soon after the lights were switched on (Fig. 1, B and C), and indeed the body temperatures for the day period after pyrogen injection at 1630 or 2100 were not significantly different from those after saline injections ($P > 0.05$, paired $t$-test; Table 1).

Figure 1 also shows that the rats exhibited a transient hyperthermic response after all injections associated with handling and the injection procedure. Irrespective of the time of injection or what was injected, body temperature rose by $\sim 0.8^\circ C$ immediately after handling and injection. This hyperthermic response lasted $\sim 90$ min, after which body temperature reverted to the normal circadian pattern when the rats were given saline. Of particular interest too is the paradoxical disturbance to body temperature that occurred in rats at the approximate time of the morning injection, even when no injections took place then (Fig. 1, B and C).

Table 1 shows other characteristics of the fever response to $S. aureus$ injection to various times of the light and dark cycle. The onset of the fever response was significantly more rapid ($P < 0.05$, unpaired $t$-test) when fever was induced at the time (1630) when body temperature was on a circadian rise compared with induction when it had reached the nighttime plateau. The time to reach the peak temperature, however, was not different between the three times of injection (ANOVA, $F = 0.837$). Most noteworthy, however, was the observation that, irrespective of the time of injection, the peak body temperature attained after the pyrogen was injected was almost identical, that is, body temperature rose to 39.0 or 39.1°C. Because, in the absence of pyrogen injection, mean daytime body temperature is significantly lower than mean nighttime body temperature, ($P < 0.05$, unpaired $t$-test), we expected that the change in body temperature after the 0900 injection of $S. aureus$ would greater than that which occurred after either the 1630 or 2100 injections. Table 1 shows the maximum changes in body temperature, which were, however, not statistically significantly different (ANOVA, $F = 0.811$).

We calculated DTRI for the first 12 h after the injection time by subtracting the body temperature response of each rat to $S. aureus$ cell wall injection from its own response to saline injection (Fig. 3). For each time of injection, the 12-h DTRI was significantly greater than zero, indicating that significant fever responses had occurred in the first 12 h after injection. The DTRI after the 0900 injection was significantly greater ($P < 0.01$, Student-Newman-Keuls) than those after both the 1630 and 2100 injection times. Thus, even though the peak temperature and the maximum change in temperature were not different for the three injection times, the nature of the fever indeed did differ; the thermal response index takes into account not only height, but also duration of fever. Thus the rats experienced a more sustained fever after the 0900 injection.

### Activity measurements.

Table 1 shows mean daytime activity counts for the rats when injected with saline or

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**Figure 1.** Body temperatures of rats before and after intraperitoneal injections of *Staphylococcus aureus* cell walls (○) and saline (○) at 0900 (A, $n = 5$), 1630 (B, $n = 8$), and 2100 (C, $n = 8$). Arrows, times of injections; bars, periods of darkness.

(see below). Body temperature of the rats injected with saline or without any intervention fell soon after the start of the 12-h light period and remained low until the onset of the dark period at 1800. *S. aureus* injected into rats at 0900, coinciding with the falling phase of the rat’s circadian rhythm, induced a rise in body temperature that eliminated the circadian difference between mean daytime and mean nighttime body temperatures and resulted in a significantly elevated body temperature for the 12 h of daytime ($P < 0.01$, paired $t$-test) compared with the equivalent temperature after saline injection at 0900 (Fig. 1A). The fever subsided by nighttime such that the mean nighttime body temperatures after the saline and pyrogen injections were not significantly different ($P > 0.05$, paired $t$-test, Table 1).

When the rats were injected with *S. aureus* cell walls at 1630, just before the nighttime rise in body temperature, or at 2100, the beginning of nighttime plateau of body temperature, body temperature rose significantly above that expected for that time of the 24-h period ($P < 0.01$, paired $t$-test; Fig. 1, B and C, Table 1).
S. aureus. Daytime activity always was significantly lower ($P < 0.01$, unpaired $t$-test) than nighttime activity after saline injections and after injections of S. aureus at 0900 and 1630, once again confirming the circadian variation in activity of rats. Mean nighttime activity was not affected by injections of S. aureus at 0900 or 1630, compared with saline injections, but activity was reduced significantly by an injection of S. aureus at 2100 ($P < 0.01$, paired $t$-test; Table 1). Injection of S. aureus had no significant effect on daytime activity of the rats, even when they were injected at 0900.

Figure 2 shows the mean activity counts for the three injection times for both S. aureus cell wall- and saline-injected rats. In a way reminiscent of the hyperthermic handling responses seen in Fig. 1, handling and injection procedures induced a transient activity spike in the rats, whatever was injected. Activity then decreased rapidly to follow circadian activity rhythms. There also was a paradoxical transient increase in activity at 0900, even when the rats were not actually injected then.

In a way similar to the way that we calculated DTRIs, we calculated DARIs by subtracting activity changes that occurred after injection of sterile saline from the changes that occurred after injection of S. aureus cell walls in the same rat at the same time. A significant decrease in activity ($P < 0.01$, paired $t$-test) over the 12 h was evident only when the pyrogen injection was made at 2100, that is, during the nocturnal period of higher activity.

**DISCUSSION**

We have shown that cell walls of gram-positive S. aureus, injected intraperitoneally into rats, induce fever, irrespective of the circadian phase at which the pyrogen is administered. Indeed, our results show two remarkable similarities in the nature of the fever generated at different phases of the circadian cycle; it took the same length of time to reach the peak temperature (Table 1), and, more importantly, the peak body temperature attained after injection of $2.5 \times 10^9$ cell walls of S. aureus varied by only 0.1°C whether the pyrogen was administered at 0900, when rat body temperature was falling, at 1630, just before the evening rise in body temperature, or at 2100, during the highest phase of body temperature. In this respect, our findings are similar to those of Satinoff and colleagues (6), who injected prostaglandin E$_1$ into rats during the day or...
during the night. In their hands too, body temperatures rose to the same level. Subsequently, Severinsen and Oritsland (32), using gram-negative LPS as pyrogen, also found that rat body temperature rose to the same degree whether the injections of LPS were made at 0900 or 1700. Our experiments have extended the earlier studies by showing that with a third pyrogenic stimulus, the gram-positive pyrogen of *S. aureus*, given at three (rather than 2) different times of the circadian body temperature cycle, the same peak fever can be attained.

There is another study in rats examining the effects of pyrogen injection made at two different times of the 24-h body temperature cycle. Sugimoto et al. (33) found that rats with significantly different preinjection temperatures had similar increases in body temperature in response to LPS, implying that different peak temperatures were attained when the pyrogen was given at nighttime compared with daytime. Actual values for peak body temperatures reached were not given, however. We have no explanations as to why these results differ from ours and other work on rats.

The fever we induced by injection of *S. aureus* cell walls lasted ~8–10 h so that day fever virtually had resolved by the night and night fever by the next day. Thus we found that nighttime body temperatures were not significantly affected by injecting *S. aureus* in the morning, and the subsequent daytime body temperatures were not affected when *S. aureus* injections were given the previous evening or night. Nomoto (24) has shown that LPS fever induced in pigeons during the day or night does not disrupt the normal circadian body temperature rhythm, and our results confirm those observations made in a species that has a reverse circadian pattern to that which prevails in rats.

The peak body temperature rise may not have been affected by the time of injection, but we have shown that the nature of the fever response was. The thermal response index takes into account not only the height of the fever, but the duration also, and so is a more comprehensive index of fever magnitude than is peak fever. Figure 1 illustrates that the fever induced by pyrogen injection at 0900 exhibited a more sustained departure of temperature from the circadian rhythm than did the fevers induced later in the 24-h cycle, and Fig. 3 confirms statistically that that was indeed the case. Thus in our rats, a greater fever response resulted when pyrogen was injected at a time when body temperature was lowest, even though the peak temperature reached was the same.

Nomoto (24) has reported that in pigeons, which have a circadian body temperature variation about twice that of rats but with body temperatures highest in the daytime, that peak fever after a fixed dose of pyrogen was higher in the daytime. He did not calculate a thermal response index, but the area under his temperature-time curve appeared greater at nighttime. Thus for pigeons, too, the overall fever response appeared more substantial when body temperature normally was lowest in the birds. Although humans have a weaker circadian body temperature rhythm than do pigeons, but also with body temperature declining at night, LPS administration produced significantly greater fevers at night in a group of normal volunteers (26).

What regulates the extent to which fever rises and how long fever endures is still a matter of speculation. Even less understood is the limitation of fever, once initiated, at different times of day. Pollmacher et al. (26) have suggested, based on measurements of cytokine concentrations in plasma of their febrile human subjects, that there may be different sensitivities to cytokines within a 24-h period, a possibility that is deserving of further investigation.

A discussion as to whether there is a regulated body temperature to which fevers, resulting from the same pyrogenic stimulus, rise, irrespective of the preinjection body temperature, was initiated by Satinoff and co-workers (6), who asked whether fever was a regulated rise in body temperature or a rise in regulated body temperature. Studies other than that, which support the notion of a regulated level to which body temperature rises during fever, are those of Kent et al. (14), who exposed rats to different ambient temperatures that affected the body temperature at which injections of live yeast organisms were made, Szelenyia et al. (34), who varied ambient temperature before intracerebroventricular injection of prostaglandin, and Conn et al. (3), who exercised hamsters to manipulate the body temperature before injecting LPS. Our results are of limited use in the debate, because the preinjection body temperatures of our rats at the three different times of day at which injections were made were not significantly different. Also, Satinoff’s arguments were based on peak temperature measurement, and our results clearly show that fevers can be significantly different even when peak temperatures are the same.

We observed not only a fever response in our experimental animals, but another form of hyperthermia too. Handling and the injection procedures resulted in a transient increase in body temperature and activity. The effects were short-lived and quite distinct from the fever response itself (Figs. 1 and 2). The rise in body temperature with handling and other procedures is well documented (2, 5, 20). Intriguing was the observation that clear, albeit lesser, hyperthermic responses occurred in the experimental animals, at a time close to that of one of the injections (0900), even when no injections took place. One explanation is that human activity in the laboratory disturbed the animals (rats in other cages were being injected in accordance with the randomized design) and resulted in a stress response even in the animals not actually handled at all. Another explanation is that some of the animals already had had injections at 0900 on a previous occasion and that they anticipated an injection at that time. Either way, the responses shown in Fig. 1 confirm the presence of anticipatory hyperthermia, first described by Eikelboom (5). Also, either way, we should have expected similar anticipatory events around the times of the 1630 and 2100 injections, but they were
either absent or masked by the higher temperatures and activities prevailing then.

A decrease in physical activity is part of the suite of responses accompanying the thermal effects of pyrogen injection, collectively known as sickness behavior (11). Other aspects of this entity include anorexia, lethargy, depression, sleepiness, reduced social interaction, and hyperalgesia (22). Physical activity was significantly decreased in our rats when *S. aureus* was injected at night (Figs. 2 and 3, Table 1), a time when activity normally is at a maximum in rats (12, 17, 29). There was no detectable inhibition of activity in rats made febrile at a time when activity normally would be at a low level, 0900 or 1630, although the lack of effect after the 1630 injection may be surprising, because the injection was made just before the evening onset of increased activity. The inhibitory effects on activity may be more transient than the thermal effects of pyrogen injection, and our results would support that conclusion. In contrast, Kozak et al. (18) found that both day and night activity in mice was inhibited after daytime LPS injection. There was no evidence in our study of a transient increase in activity in the rats before the suppression of activity in response to pyrogen injection of the kind previously reported by Romanovsky et al. (27).

The decreased activity, which now seems to be a response to any pyrogen, may be a host defense strategy to minimize metabolic energy expenditure (11), but it also may lead to other consequences, such as the decreased food and water intake observed following injections of pyrogens (18). Whereas a considerable amount now is known about the role of cytokines in generating the thermal effects during infection (15), much less is known about the mediators of the components of sickness behavior. Certain cytokines, such as interleukin-1α (IL-1α) (25) and tumor necrosis factor-α (TNF-α) (1), which are pyrogenic in rats and mice, also reduce physical activity when administered to these animals. A case has been made for IL-1α as the mediator of the inhibition of social and grooming behavior during fever (1) and of the anorexia of sickness behavior (13). Whereas injection of IL-1α into rats inhibited locomotor activity (23), IL-1α knockout mice do not show reduced capacity to suppress activity after LPS injection (18). Although interleukin-6 (IL-6) seems to have a role in mediating the anorexia during inflammation, it appears not to be the mediator involved in the suppression of activity either, because IL-6 knockout mice have no less inhibition of activity in the early phase after injection of turpentine oil than do normal wild-type mice (16).

Sickness behavior accompanies natural infection (11), and, up to now, has been induced experimentally most frequently by gram-negative LPS injection, but also can be induced by injection of turpentine oil, influenza virus (16), and some cytokines themselves (see above). We provide here the first evidence that sickness behavior, as shown by the suppression of physical activity, also occurs in response to experimental gram-positive infections too. Gram-positive cell walls in vitro cause release of endogenous pyrogens similar to those thought to be released in response to gram-negative bacteria (35). There are differences, however, in the fevers induced by gram-negative and gram-positive bacteria, such as the difference in responses to the two pyrogens in parturient animals (9), their different ability to induce tolerance after repeated injections (8), and the fact that gram-positive bacterial fever may involve mediators other than those released after gram-negative stimulus (7, 22, 28). Our results imply that the mechanisms responsible for induction of sickness behavior are common to both gram-negative and gram-positive bacterial infection or that a considerable variety of endogenous mediators, including muramyl dipeptide, which mediates gram-positive febrile responses at least in part (7, 28), have that ability. In any event, our results provide evidence that sickness behavior is a ubiquitous accompaniment of fever and appears not to be specific to any one exogenous pyrogenic agent.

In summary, we have shown that the gram-positive organism *S. aureus* causes fever in rats and that the height of the fever response is not affected by the time during the rat’s 24-h temperature cycle when the pyrogenic stimulus is given. Nevertheless, we have found that the intensity of the fever, as characterized by the height and duration of the febrile response, is greatest during the time of the rat circadian body temperature cycle when body temperature normally is at its lowest. In addition, we have provided the first evidence that sickness behavior accompanies experimentally induced gram-positive bacterial fever; we found that physical activity was suppressed during *S. aureus* fever, but only at that time of the activity cycle when activity in the rats normally was high.

**Perspectives**

Our results have implications for fever in humans. If the level of febrile body temperature attained is the same or similar at various times of the 24-h period in humans, as it appears to be in rats, then fevers will be most noticeable as a deviation from normal body temperature at the time when body temperature normally is low, that is, at night. Not only so, but the fever itself may be longer lasting at night, and thus patients would experience a more intense febrile episode then too; it is a common observation of parents, and one that is well documented (21), that most fevers in children occur at night. There are consequences for the management and treatment of patients with fever too. For example, one may require more aggressive management of sickness behavior at night, including increased analgesia for conditions resulting in fever and pain concurrently, and antipyretic therapy may need to be intensified at night. Of consolation to caregivers and patients alike is the prediction that the arrival of a new phase of the circadian body temperature rhythm may signal the demise of an acute fever.

We thank David Makoa and Debbie Angus for help with the experiments and data analysis, G. Hardy and E. Marcos for assis-
REMARKS

tance in the preparation of the S. aureus, the Central Animal Service
for assistance with the surgery and care of the animals, and Dr. T.
Cartmell for helpful comments on the manuscript.

The work was funded by the South African Medical Research
Council and the University of the Witwatersrand.

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