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Activity-based anorexia: Ambient temperature has been a neglected factor

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Activity-based anorexia refers to the self-starvation of rats exposed to experimental conditions that combine restricted access to food with access to an activity wheel. This paper compares previous studies of this phenomenon in relation to the ambient temperatures (AT) that were employed. On this basis, and from some more direct evidence, we argue that AT is an important, but neglected, factor in activity-based anorexia research. More attention to AT is needed in future research, since its neglect threatens the validity of conclusions drawn from those studies. Furthermore, direct examination of the effect of AT on activity-based anorexia will allow a better understanding of the mechanisms underlying this phenomenon and the possible clinical implications for the treatment of human anorexia nervosa.

When rats are simultaneously placed on a restricted feeding schedule and given free access to an activity wheel, they can self-starve. That is, their body weight can progressively decrease to the point where they will die unless removed from the apparatus (Routtenberg & Kuznesof, 1967). Under these conditions, the rats display a high rate of running activity. Furthermore, while activity steadily increases on a daily basis, rats show paradoxically reduced intake of food during the single daily feeding period, when compared with control subjects without access to a running wheel. The combination of reduced food intake and increased activity can produce self-starvation within a few days.

The present paper focuses on an environmental factor, ambient temperature (AT), that is known to be important to the relationship between activity and weight loss but has received relatively little attention. One aim is to review the experimental evidence on the effect of AT on the self-starvation outcome of activity-based anorexia experiments. A second aim is to develop an account of increased running in terms of surrogate thermoregulatory behavior triggered by rat's hypothermia. A final aim is to propose a new perspective on the role of excessive activity in human anorexia nervosa, pointing to the use of external heat in the treatment of anorexia nervosa when hyperactivity is a salient feature.

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ACTIVITY-BASED ANOREXIA AS AN ANIMAL MODEL OF HUMAN ANOREXIA NERVOSA

Epling, Pierce, and Stefan (1981) introduced the term *activity-based anorexia* for both the experimental procedure and the behavioral outcome. The procedure is also commonly referred to as the *activity-stress paradigm* in research focused on ulcer formation in the glandular portion of rats' stomachs (Paré & Houser, 1973). Such ulceration is often produced when the combination of restricted feeding and wheel access causes weight loss exceeding 30%. Ulceration is rarely seen with weight losses of less than 25%, the criterion for removing animals from an experiment that is normally used in activity-based anorexia research in which ulceration is not of primary concern (Doerries, Stanley, & Aravich, 1991). This paper reviews experiments done with rats in which it was reported that either *activity-based anorexia* or *activity-stress* procedures were used. We concentrate on increased running, decreased food intake, and weight loss produced by the procedures rather than on ulceration or other physiological changes.

The paradoxical increase in activity shown by rats exposed to restricted feeding and subsequent self-starvation and weight loss provides an interesting parallel with the symptoms of human anorexia nervosa, such as hyperactivity, voluntary food restraint, and weight loss (Epling & Pierce, 1991, 1996; Pierce & Epling, 1994). Furthermore, the experimental procedure produces other effects in the rat (e.g., hypothermia, loss of estrous, the disruption of circadian pattern, and some metabolic abnormalities)

that suggest its potential value as an animal model for human anorexia nervosa.

Hyperactivity in Anorexia Nervosa

Observation of excessive activity in anorexic patients has been reported ever since the first description of human anorexia. From accounts centuries ago of anorexia related to religious belief (Bell, 1985) to contemporary clinical studies, high levels of activity in anorexia are very commonly noted, as in the early case reports by Gull (1874) and Lasègue (1873). In his presentation to the Clinical Society of London in 1873, Gull stated:

> The patient complained of no pain, but was restless and active . . . it seemed hardly possible that a body so wasted could undergo the exercise which seemed agreeable. (p. 23)
>
> The restless activity referred to is also to be controlled, but this is often difficult. (p. 25)
>
> The great difficulty was to keep her quiet. She was most loquacious and obstinate, anxious to overdo herself bodily and mentally. (p. 27)

Surprisingly, those young girls did not feel tired, but even energetic. As the mother of Case B said, "She is never tired" (p. 24). In the same year, Lasègue (1873) commented on this aspect:

> Another ascertained fact is, that so far from muscular power being diminished, this abstinence tends to increase the aptitude for movement. The patient feels more light and active, rides on horseback, receives and pays visits, and is able to pursue a fatiguing life in the world without perceiving the lassitude she would at other times have complained of. (p. 148)

Twentieth century studies of anorexia have noted a continuum of activity from strenuous exercise to aimless restlessness, including hyperactivity, intense work schedules, and just not allowing oneself a minute of rest. For example, an influential midcentury text on eating disorders described the different forms that hyperactivity can take, noting its precedence over eating:

> Hyperactivity is rarely complained of, or even mentioned, by the patients or the parents; but it will be found with great regularity if looked for. Detailed questioning usually reveals that the hyperactivity developed before the noneating phase. Sometimes an existing interest in athletics and sports becomes intensified. Others engage in activities that seem to be aimless, such as walking for miles, chinning and bending exercises, refusing to sit down or literally running around in circles. (Bruch, 1966, p. 272)

Similarly, King (1963) noted that anorexic patients "were overactive, always performing or seeking some task, often repeating tasks aimlessly for the sake of activity itself" (p. 475). In the first half of the 20th century, hyperactivity was the symptom used to differentiate anorexia nervosa from the diagnosis of other forms of emaciation, such us those caused by Simmonds's disease (Escamilla, 1944) and Addison's disease (Farquharson & Hyland, 1938). Curiously, however, despite such recurrent reports, hyperactivity has continued to be treated as a secondary symptom of anorexia nervosa (Feighner et al., 1972).

Further Parallels Between Activity-Based Anorexia in Rats and Human Anorexia

Unlike other forms of anorexia in animals (Mrosovsky & Sherry, 1980; Treasure & Owen, 1997), activity-based anorexia is an effect that can easily be studied in the laboratory. As noted above, the triad of excessive activity, self-starvation, and weight loss are not the only features that this laboratory model shares with human anorexia. Thus, the occurrence of amenorrhea is required for the diagnosis of anorexia nervosa in female patients, just as female rats also lose estrous as weight loss progresses (Watanabe, Hara, & Ogawa, 1990).

Hypothermia is another common feature. This was recognized by Gull (1874) as a sign of anorexia nervosa in his first description of the illness: "I have observed that in the state of extreme emaciation, when the pulse and respiration are slow, the temperature is below the normal standard" (Gull, 1874, p. 24). Hypothermia is connected with another symptom of human anorexia nervosa, nocturnal activity and wakefulness in the second half of the night (Crisp, 1985). Rats also show a change in circadian rhythm of activity as they lose weight and as body temperature decreases. Normally, rats are most active during the dark period of a day; under laboratory conditions, they sleep 2–4 times as much during the lights-on period as during the lights-off period (Ibuka, Inouye, & Kawamura, 1977). However, as rats lose weight, the amount of activity increases during the light hours. A critical point for ulceration is found when the percentage of activity during the light phase is over 50% (Watanabe et al., 1990). As previously noted, the combination of wheel access and restricted feeding, especially when weight loss is over 25%, results in stomach ulcers in rats. Stomach ulceration is a medical complication found in 16% of patients with anorexia nervosa (Hall & Beresford, 1989). Furthermore, rats meeting the 25% weight loss criteria of activity-based anorexia show a paradoxical reduction in hunger following administration of the glucose antimetabolite 2-deoxy-D-glucose, which is related to reductions in plasma glucose and insulin, three metabolic abnormalities associated with anorexia nervosa (Aravich, Stanley, & Doerries, 1995).

Although in this section we have concentrated on similarities between self-starvation in rats and human anorexia, we should note that there are also important differences. In particular, when rats are exposed to the activity-based anorexia procedure, their food intake steadily increases, although the rate of increase is often not sufficient to prevent progressive weight loss (Aravich, 1996; Dwyer & Boakes, 1997). Furthermore, rats removed from the apparatus on reaching the 25% weight loss criterion and given unrestricted access to food may show no "loss of appetite" but instead rapidly regain weight to a healthy level (Boakes, Mills, & Single, 1999; Paré, 1976). Nonetheless, we would argue on the basis of the many parallels described in this

section that the activity-based anorexia procedure provides the best animal model available for providing some understanding of many symptoms, if not initial causes, of human anorexia nervosa, especially when weight loss proceeds beyond the 25% criterion. It can also suggest new approaches to treatment.

AMBIENT TEMPERATURE IN STUDIES WITH RATS ALLOWED CONTINUOUS ACCESS TO RUNNING WHEELS BUT RESTRICTED ACCESS TO FOOD

Evidence for the modulating effect of AT on survival, running, and weight loss in rats exposed to the activity-based anorexia procedure comes from both indirect and direct experimental comparisons. Indirect evidence comes from a reanalysis of data from experiments that have dealt with other factors. After reviewing this research, we examine direct evidence from the single published experiment that has manipulated AT and from an unpublished study in which two different groups of rats were run at different temperatures.

Variations in a large number of experimental parameters affect running and weight loss in semistarved rats and so are relevant for understanding self-starvation. The rate of weight loss is much reduced and food intake greater with longer feeding periods (e.g., Paré 1980; Paré & Valdsaar, 1985; Paré, Vincent, & Natelson, 1985; Routtenberg, 1968; Routtenberg & Kuznesof, 1967; Watanabe, Hara, & Ogawa, 1992), with multiple rather than with single daily feeding periods (e.g., Lambert & Peacock, 1989; Tsuda, Tanaka, Jimori, Ida, & Nagasaki, 1981), with feeding during the dark cycle (e.g., Dwyer & Boakes, 1997; Hara, Manabe, & Ogawa, 1981; Paré, 1975; Paré et al., 1985), and with prior adaptation to the restricted feeding schedule (e.g., Dwyer & Boakes, 1997; Paré, Vincent, Isom, & Reeves, 1978; Paré et al., 1985; Routtenberg, 1968). Further procedural factors include prior exposure to the running wheel (Routtenberg, 1968), type of feeding site (Paré, 1974; Routtenberg, 1968), amount of access to the wheel (Dwyer & Boakes, 1997; Epling & Pierce, 1984; Paré, 1980), and dietary composition (Beneke & Vander Tuig, 1996).

In addition to procedural parameters, subject characteristics are also important. Thus, running and weight loss are reduced when older (Hara et al., 1981; Paré, 1975) or heavier (Beneke & Vander Tuig, 1996; Boakes & Dwyer, 1997; Yi & Stephan, 1996) rats serve as subjects. The results can also be affected by the sex of the animal (Boakes et al., 1999; Lambert & Kingsley, 1993; Paré, 1975; Paré et al., 1978; Watanabe et al., 1990, 1992), basal activity (Paré, 1975), and premorbid sensitivity to disruption of circadian temperature pattern (Morrow et al., 1997). Subjects' preexperimental experience can also be important. Such factors include individual housing, as compared with group housing (Boakes & Dwyer, 1997; Paré & Valdsaar, 1985; Paré et al., 1985), early weaning (Glavin & Paré, 1985), prior stress (Paré, 1986), and environmental enrichment (Paré & Vincent, 1989). Finally, increased activity resulting from food restriction has been observed in different rat strains and in other species of rodents (Epling et al., 1981; Hara & Ogawa, 1984; Paré, 1989; Pierce & Epling, 1991; Vincent & Paré, 1976; Watanabe et al., 1990, 1992).

Rats' Survival Under Restricted Feeding and Wheel Access as a Function of Ambient Temperature: Indirect Experimental Evidence

The influence of different AT levels on survival rates for different groups of rats can be inferred from a set of experiments that have focused on ulceration produced by the activity-based anorexia procedure. These experiments were carried out in the same laboratory and by the same principal investigator, Paré, between 1973 and 1985 (see Table 1), except for the first two studies listed in Table 1. Almost all

Table 1
Influence of Ambient Temperature on Rate of Survival Under Restricted Feeding and Wheel Access

Study	AT (°C)	Weight (g)	*N*	Reported Survival Rate After Days of Experiment
Houser et al., 1975*	19.5	130–177	20	65%, 43%, 10%, and 0% after Days 3, 4, 5, and 6
Lambert & Porter, 1992 (Exp. 2)**	21–22	200–250	35	Mean survival of 7–8 days; 0% survival after 14 days
Paré, 1977a (Exp. 2)	22	188–210	12	0 % after Day 7
Paré, 1975 (Exp. 2)***	23	201–227	8	High active rats: 0% after 15 days
			7	Low active rats: 43% after 15 days
Paré, 1978	23–24	194–248	30	Mean survival of 10 days; first casualty on Day 6
Paré, 1977b (Exp. 1)	23–24	210–256	20	40% after 21 days
Paré, 1976 (Exp. 1)†	23.3–24	160–195	30	3% after 17 days
Paré et al., 1980‡	23.3–24	183–222	10	80% , 60%, 40%, and 0% after Days 7, 8, 9 and 10
Paré, 1975 (Exp. 4)	23.3–24	96–109	30	20% after 21 days, first casualty on Day 4
Paré, 1975 (Exp. 2)	23.3–24	190–215	34	82% after 12 days; 30% after 21 days
Paré, 1975 (Exp. 4)	23.3–24	192–212	30	29% after 21 days
Paré, 1975 (Exp. 1)	23.3–24	214–224	17	83% after 12 days; 29% after 21 days
Paré, 1975 (Exp. 4)	23.3–24	289–305	30	60% after 21 days
Paré & Houser, 1973	23.3–24.5	250–279	18	44% after 21 days
		352–400	18	72% after 21 days
Paré, 1974	23.3–24.5	218–248	18	75% after 12 days; 45% after 21 days

*Rats received saline injections and 2 days of habituation to the wheel. **Rats (Long-Evans strain) received saline injections and 4 days of habituation to the wheel. ***Rats selected from a group of 40 according baseline activity (10 days of habituation to the wheel). †Five days of habituation to the wheel. ‡Rats removed 24–48 h before impending death (peak running, food intake decay, and sharp weight decrease).

groups consisted of rats of the same sex and strain (male Sprague-Dawley rats), of comparable weight (range across studies, 188–279 g), without preadaptation to the wheel, and were fed the same food (granular Purina Rat Chow). Also, all groups had 23-h free access to a wheel and the 1-h feeding period was at the same time of day for all groups, from 0900 to 1000 during the same 12:12-h light:dark cycle (lights on from 0600 to 1800). The few exceptions are listed in the note to Table 1. Comparisons with other experiments that have used the same basic procedures are less productive because variations in many of the parameters outlined in the previous section are confounded with differences in AT (see the Appendix).

For unknown and presumably incidental reasons, the experiments shown in Table 1 were carried out under different ATs, ranging from 19°C (Houser, Cash, & Van Hart, 1975) to 23.3°–24.5°C (Paré, 1974; Paré & Houser, 1973). Although this range may appear narrow, different temperatures were associated with different mortality outcomes. As can be seen in last column of Table 1, survival rate increases as AT increases. Moreover, for the range of weights reviewed, the effect of AT seems even stronger than either the effect of low body weight or prior exposure to the wheel, two factors associated with lower survival rates. This between-experiments evidence for the role of AT in rats' survival rates indicates the need for within-experiment control of this factor in order to clarify the way it may modulate important variables such as running, food intake, and weight loss.

Rats' Survival Under Restricted Feeding and Wheel Access as a Function of Ambient Temperature: Direct Experimental Evidence

The importance of AT was suggested by an unpublished experiment in which a large, but accidental, change in temperature was caused by a malfunctioning thermostat. This temperature change appeared to produce a major effect in an experiment focused on ulcers (Lambert, 1993). Rats accidentally given an AT of 25.6°C ran less than rats given the planned temperature of 22°C, a difference that was significant in a post hoc analysis. This serendipitous finding motivated a planned experiment, the results of which were reported in an unpublished conference paper (Lambert & Hanrahan, 1990). In that experiment, 44 male Long-Evans rats (47 days of age) were matched by weight and were randomly assigned to one of four groups in a 2×2 factorial design. All four groups were placed on a restricted feeding schedule, with two *active* groups given access to a running wheel and two *nonactive* groups without wheel access. The second factor was whether the groups were housed in a 25°C or in a 19.4°C environment. The amount of food available to the nonactive rats was yoked to the amount eaten by the active rats. The results of that study confirmed those from the "accidental" study. Rats in the warm environment differed significantly from the rats in the cool environment with respect to wheel running and ulcer incidence. As for survival rates, the cool, active animals started dying on Day 3 of the procedure, and all were dead by Day 6. However, the warm, active animals started dying on Day 5, and 3 animals survived the entire 14-day period of the study. These differences in survival were statistically significant.

Further direct experimental evidence of AT on rats' survival comes from a study in which 60-day-old female Sprague-Dawley rats were exposed to the standard experimental procedure (1-h feeding plus wheel access) after a period of habituation to the wheel under ad lib feeding (Morrow et al., 1997). AT was maintained at 21° ± 0.5°C. Four groups of rats received a different manipulation as they reached a criterion of impending death while on the restricted 1-h feeding. Twenty-four hours prior to becoming hypothermic and moribund, various groups were left undisturbed ($n = 18$), warmed with a heat lamp ($n = 9$), denied access to running wheels ($n = 13$), or were euthanased ($n = 8$). A fifth, control group of rats was maintained on a restricted feeding schedule, but were never given access to the running wheel.

Sixty percent of the heat lamp group (AT changed from 21°C to 37°C) survived the experimental conditions for a week in this warmer environment. This group even outlived, on average, the food-restricted controls that never had access to a running wheel (11.1 days). The mean number of survival days for the heat lamp group, 12.2 days, was more than double that for the group continuously exposed to the experimental procedure, 4.8 days, and for the group whose wheels became locked, 5.3 days. So, despite the food restriction and continued access to the wheel, AT showed a potent modulating role on survival rates under the experimental conditions. Morrow et al. (1997) also found that, once marked weight loss had occurred, the denial of access to the wheel was not sufficient to keep the rats alive (average survival of 5.3 days vs. the 4.8-day average survival for those rats left undisturbed). In the terminal stage, rats completely self-starved before dying from gastrointestinal hemorrhages (Paré, 1976) or from viral infections due to immune deficiency (Hara et al., 1981). Once rats are near to death, only two possibilities have proved effective in prolonging survival: either the combination of denying access to the wheel and giving unrestricted access to food (Paré, 1976) or maintaining wheel access and restricted feeding, but increasing AT (Morrow et al., 1997).

The close connection between weight loss and decreased food intake is important here in light of Brobeck's (1960) recommendation that "one cannot study food intake without specifying or controlling the conditions of temperature regulation" (p. 448). However, many experimental reports have failed to specify the AT and, where this factor is reported, there has been considerable variability within and among experiments (see the Appendix). This raises problems both with respect to the internal validity of the experiments and to comparisons across experiments.

EXCESSIVE RUNNING ACTIVITY AS A SURROGATE THERMOREGULATORY BEHAVIOR

The excessive activity of food-restricted rats has fascinated researchers ever since it was first observed. As de-

tailed in a recent review (Sherwin, 1998), attempts to account for increased activity in hungry rats include considering it as schedule-induced behavior (Levitsky & Collier, 1968), as foraging behavior (Spatz & Jones, 1971), and as a product of various physiological mechanisms (Aravich, 1996; Pirke, 1996; Russell & Morse, 1996). One approach to understanding the increased running produced by food restriction is related to a key assumption of Brobeck's (1945, 1948) thermostatic theory. This theory proposes that all aspects of energy exchange are regulated through their effect on temperature regulation. Following this proposal, increased running by food-restricted rats in a cool environment can be seen as a strategy to cope with the threat to maintenance of core body temperature. Seen from this perspective, increased running could be a mechanism for avoiding the decrease in body temperature that might otherwise occur due to reduced food intake (Lambert, 1993; Morrow et al., 1997; Paré, 1977a; Paré & Vincent, 1981).

An early, and extreme, version of this theory, whereby *all* spontaneous running is explained in terms of thermoregulation, was discredited by the finding that some running occurred even at high ATs that were well above rats' thermoneutral zone (Campbell & Lynch, 1967, 1968). The version proposed here is that *increases* in running produced by food restriction are related to thermoregulation (Paré, 1977b). Recent proposals of this kind have either been rejected (Morrow et al., 1997) or disregarded in favor of alternative mechanisms based on mesolimbic dopaminergic activity (Lambert, 1993). We would argue that evidence for the effect of AT on mortality suggests that it would be premature to abandon the search for a link between the self-starvation effect and thermoregulation.

Spontaneous running in food-deprived rats could serve the same thermoregulatory function as instrumental behavior, reinforced by onset of a heat lamp, of rats exposed to a cold environment (Carlton & Marks, 1958; Weiss & Laties, 1961). Under such experimental conditions, rats work harder for heat when deprived of food (Hamilton, 1959; Weiss, 1957) and when the intensity or duration of bursts of heat are reduced (Weiss & Laties, 1960). Additional early evidence suggesting the thermoregulatory nature of activity is the finding that restriction of activity decreased the rectal and skin temperatures of food-deprived rats (Stevenson & Rixon, 1957). Moreover, in rats with unrestricted access to food that were exposed to temperatures ranging from 5°C to 33°C, the rate of increase and peak in running activity depended on the surrounding AT, being greatest in the cold environment (Stevenson & Rixon, 1957). The instrumental role of activity in the maintenance of body temperature is also suggested by restraint stress: Hypothermia is one result of a procedure that involves a period of 1–5 h of immobilization, following a period of 12 h or less of prestress food deprivation (Paré & Glavin, 1986).

However, thermoregulation cannot be the only factor contributing to increased wheel running in rats. One reason is that increases in running occur prior to any detectable drop in body temperature (Morrow et al., 1997). A further reason, already mentioned, is that increased running with food restriction has been found even when hypothermia was prevented by a high AT of 31°C (Campbell & Lynch, 1967) and when access to a warmer chamber held at a constant 35°C was available (Campbell & Lynch, 1968). Such results suggest that initial increases in activity depend on factors other than temperature regulation. Thus, there is continuing controversy over the initial development of wheel running in rats and other species. Currently, the most convincing account is that provided by the conclusion of a recent review:

> In many instances, although wheel running may be an artifact of the laboratory environment or of the wheel itself, it nonetheless is self-reinforcing and is (sometimes) performed as a behaviour in its own right, rather than as a substitute or redirected behaviour." (Sherwin, 1998, p. 23)

What is of most interest here is not the initial phase of activity, but the phase when weight loss has already progressed and thermal needs become prominent (Paré, 1977a). In this phase, a relationship between thermoregulation and running is strongly indicated by a number of findings.

In procedures offering a choice between running and a response that will produce more warmth, it has been found that once body temperature has begun to decrease following progressive food deprivation, running might decrease as well. This has been found both when the alternative to running is an instrumental response that switches on an infrared lamp (Hamilton, 1969; Hamilton & Brobeck, 1964) and when the alternative is a warm chamber (Campbell & Lynch, 1968).

In contrast to less energy-expensive ways of increasing body temperature, such as switching on a lamp or entering a warm chamber, thermoregulatory running eventually results in a further decrease of body temperature. Although bursts of running produce increases in body temperature (Campbell & Lynch, 1967; Morrow et al., 1997; Thompson & Stevenson, 1963), the mobilization of fat reserves employed to sustain activity is made at the expense of a reduction in body insulation from the environment. Thus, running further stretches the capacity of the body's thermoregulation system. This process is made more deleterious by the constraints on adequate energy replenishment exerted by the restricted feeding schedule (Paré, 1977a). The dangerous cascade of changes following the attempt to remedy hypothermia by increasing activity is depicted in the lower part of Figure 1.

The upper part of Figure 1 represents an individual difference factor that seems to act as a predisposing characteristic for entering the vicious cycle depicted in the lower part of the figure. Rats showing above average variability in body temperature during the first day of food restriction are less likely to survive the procedure (Morrow et al., 1997). Early weaning also makes rats more vulnerable to the procedure, in that such rats display higher mortality and ulcer formation (Glavin & Paré, 1985). Early weaning also increases the thermoregulatory disturbance produced by stressful restraint procedures (Ackerman, Hofer, &

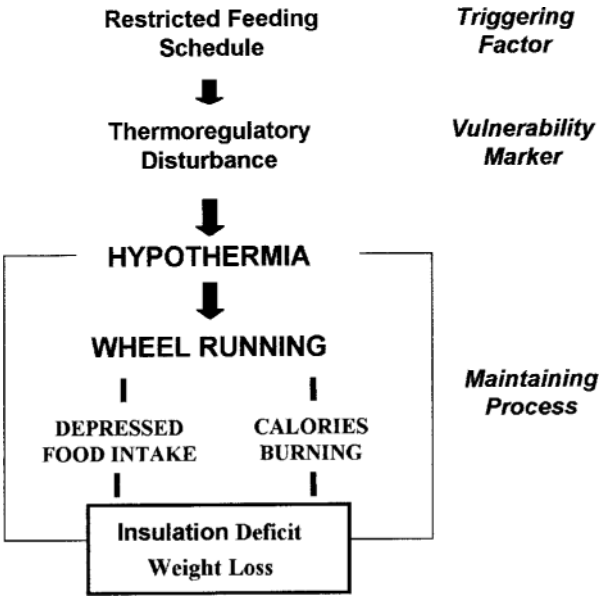

Figure 1. Diagram showing the vicious cycle between thermoregulatory wheel running and hypothermia in research on activity-based anorexia.

Weiner, 1978). Furthermore, normally weaned rats that are less successful in regulating or restoring their body temperatures in the poststress period (after supine or water restraint) are also those showing greater ulceration (Paré, 1988). Overall, thermoregulatory disturbances could be a marker for vulnerability to the self-starvation effect, one that is triggered by stress resulting from the change from unrestricted to restricted feeding. The increased running displayed to compensate for this disturbance would set in motion a process that maintains the "vicious cycle."

AT as a Protective Factor Against Activity-Based Anorexia

The hypothesis that hyperactivity is linked to hypothermia predicts that activity will be lower at higher temperatures because a warm environment reduces heat loss. This prediction is consistent even with experiments in which the results have been seen as inconsistent with the claim that running has a thermoregulatory function. Thus, although Campbell and Lynch (1967) found that running increased with food deprivation even in rats housed at a very high temperature (31°C), the amount of running on most activity days was less than 2,000 wheel turns. In comparison, in a similar experiment carried out by these authors, using rats of the same sex, weight, and strain, but maintained at an AT of 20°C, the amount of running was three times that of the rats housed in the 31°C environment. Furthermore, they lived an average of only 4.5 days (Campbell & Lynch, 1968). On the other hand, in the experiment run at 31°C, peak activity for the 5 rats was much delayed, in that 1 rat was most active on the fourth day, 2 on the fifth day, and 2 on the sixth day (Campbell & Lynch, 1967).

A low level of running activity has also been reported in studies run at temperatures above 24°C, but well below the 31°C used by Campbell and Lynch (1968). Thus, in an experiment intended to be run at 26.6°C, but which, due to poor temperature control, increased to 28°C on some days, Bolles and Duncan (1969) reported fewer than 500 turns a day (equivalent to 280 m/day due to the small size of the wheel). An unusually low level of running in a group of rats (mean weight 255 g and fed 1.5 h daily) was also reported by Altemus, Glowa, Galliven, Leong, and Murphy (1996) in an experiment using a high AT level (24°C). The mean daily wheel turns for this group of female rats—females are usually more active than males (Boakes et al.,1999; Lambert & Kingsley, 1993; Paré, 1975; Paré et al., 1978; Watanabe et al., 1990)—never reached 4,000 m on any day. This is in sharp contrast with the high levels of running, very often over 10 km/day, commonly found in food-restricted rats given wheel access in the 20°–22°C range of temperatures (Lambert, 1993; Paré, 1980).

An inverse relation between AT and running is potentially important for the self-starvation effect, since it would mean that the reduction in running produced by a high AT would lead to lower energy expenditure (see Figure 1). Thus, the rate of weight loss would be reduced and the animals would be able to survive longer. Such a protective role was seen in the Lambert and Hanrahan (1990) study, in which warmer rats ran significantly less and survived longer than did cool rats. Furthermore, as noted above, in Morrow et al. (1997), warming rats from 21°C to 37°C at the first signs of impending death not only significantly increased their survival rates but also stabilized their weights. Furthermore, by the time that they were sacrificed, their running had returned to its previous baseline level.

The effect of AT on activity obviously could prevent one of the well-known side effects of excessive activity for a semistarved animal—namely, the reduction of food intake by exercise (Rivest & Richard, 1990). Experiments in which exercise has been enforced have shown that by increasing exercise, food consumption is decreased, and that this effect increases when feeding is restricted to one 3-h meal/day (Stevenson, Box, Feleki, & Beaton, 1966). This inhibitory effect of exercise on food intake is shown by the transient decrease in food intake when groups of rats fed ad lib are introduced to the wheels (Altemus et al., 1996). Furthermore, Pierce, Epling, and Boer (1986) showed that both spontaneous and forced activity can decrease the reinforcing effectiveness of food, as if "exercise appears to substitute for eating" (Epling & Pierce, 1991, p. 144). The brain mechanism underlying this anorexic effect of exercise seems to involve the hypothalamic–pituitary axis (Rivest & Richard, 1990).

Added to the constraint imposed by the restricted feeding schedule, depressed feeding provides a further obstacle to adequate energy replenishment. On the other hand, the suppression of excessive activity caused by a warm environment—either by preventing it from becoming excessive (Lambert & Hanrahan, 1990) or by reversing it when

peak levels are attained (Morrow et al., 1997)—will, respectively, impede or release the subsequent depressant effect of activity on food intake. Thus, an increase in AT will have both a direct preventive effect on weight loss and an indirect effect on feeding, because once strenuous activity is blocked, so is its interference with feeding. Thus, in the study by Morrow et al., the food intake of warmed rats (37°C) matched that of the control nonactive group, despite the fact that the heat lamp was turned off during the feeding period. Also in Lambert and Hanrahan's unpublished study, food intake in the cool group was less than that in the warm group, although the difference did not reach statistical significance. This lack of a reliable difference between the cool and warm groups might have occurred because the AT for the latter group (25°C) was not very much higher than the AT levels commonly used in activity-based anorexia studies (see the Appendix). In contrast, the AT of 37°C in Morrow et al. was clearly beyond the thermoneutral zone, (27°–31°C; Gordon, 1990), which is defined as the AT at which the basal rate of heat production equals the rate of heat loss to the environment, and a minimal amount of thermoregulatory effort is required to maintain a constant body temperature. In combination, the two experiments suggest the possibility that the maximum protection for the self-starvation effect afforded by raising the AT might be found when the AT is in the thermoneutral range.

There may be one further way in which heat might facilitate feeding, one that operates more directly than the two already discussed. This is suggested by a study in which rats were subjected to forced swimming that was highly energy demanding (Stevenson et al., 1966). This procedure led to a reduction in food intake on exercise days, relative both to nonexercise days and to nonswimming control rats. On the 14th day, due to the malfunction of a thermostat, the AT increased from the intended 24°C to 28°–30°C for a 3-day period. The authors noted a puzzling effect during those high AT days: Food intake increased with the rise in temperature, even though the enforced heavy exercise schedule was continued. In contrast, the facilitative effect of high AT on food intake reported by Stevenson et al. appears to be a direct one; it did not involve decreased activity, since a constant level of exercise was enforced throughout. This direct effect could perhaps result from an interaction of AT with metabolic processes characteristic of the postexercise period, such as excess oxygen consumption (Richard & Rivest, 1989).

Confirmation of a direct facilitative effect of high AT on food intake would, at first glance, seem inconsistent with Brobeck's (1960) thermostatic theory, since a high AT should increase neither locomotor activity nor feeding. However, although in homeotherms food intake is inversely related to environmental temperature (Brobeck, 1960), this does not apply to rats exposed to restricted feeding, because of their hypothermia. Whether the effect of heat on food intake is indirect—via cancellation of the inhibitory effect of activity (Lambert & Hanrahan, 1990; Morrow et al., 1997)—or a direct and facilitative one (Stevenson et al., 1966), increased AT has a major effect on the self-starvation effect. In either case, the better meal efficiency and less running afforded by a warm environment seems either to prevent rats from entering the positive feedback loop linking activity and reduced food intake, or to break it once it has been established.

IMPLICATIONS FOR ANOREXIA NERVOSA

The change from an unrestricted to a restricted feeding schedule produces an initial loss of weight in all laboratory rats. The extent to which this initial drop is followed by rapid and progressive weight loss can vary considerably among rats. As reported above, there is some evidence to suggest that such individual differences can be predicted by thermoregulatory measures. Thus, thermoregulatory disturbance might provide a vulnerability marker for the final self-starvation effect. The same individual difference factor might be present in people prone to anorexia nervosa after an initial loss of weight.

In the human disorder, initial weight loss can occur for a variety of reasons. In addition to the familiar and common example of dissatisfaction with body shape, these reasons can include attempts to improve athletic performance or school grades, facing a surgical intervention, or coping with a major life event. Whatever the precipitating cause, a weight loss of 4–6 kg commonly occurs during the initial, nonspecific phase of anorexia nervosa (Bassøe, 1990). This initial loss of weight, together with the resulting hypothermia, could trigger entry into a second phase, in which symptoms of anorexia become manifest and hyperactivity (motor activity) begins to function as an alternative heat producing mechanism. In this advanced phase, there would be a thermoregulatory disorder that maintains the disorder. Thus, excessive activity in anorexia nervosa, including strenuous exercising, might be best regarded as a biobehavioral response elicited by the physiological consequences of an initial loss of weight, rather than as a willful strategy to burn calories.

From this perspective, the important point is that whatever the variant of hyperactivity that develops—whether restless activity or strenuous exercising—the muscular activity produces heat. Thus, activity is not so much a response to a disturbed body image but rather to a disturbance of thermoregulatory homeostasis and the hypothermia resulting from a significant loss of weight. However, the greater the increase in physical activity, the more likely that three consequences will follow: first, a strengthening of the inhibitory effect of activity on appetite (Blundell & King, 1999, 2000; Kissileff, Pi-Sunyer, Segal, Meltzer, & Foelsch, 1990), second, loss of body insulation due to wastage of fat stores, and third, further impairment of effective thermoregulatory homeostasis through nourishment.

Implications for Treatment Using Heat Management

Extrapolation from rats to humans always demands critical caution. However, in the present case, there is sug-

gestive clinical evidence that the application of external heat to patients with anorexia nervosa can neutralize hyperactivity and thus decrease its role in maintaining food refusal (Gutiérrez & Vázquez, 2001). When first introducing the term *anorexia nervosa*, Gull (1874) also suggested that anorexic patients be given external heat. As here, the basis for the idea came from animal studies. In his seminal presentation to the Clinical Society of London, Gull stated that it was "often necessary to supply external heat as well as food to patients" (p. 24). Gull's recommendation was based on careful observations by the Swiss physiologist Chossat (1796–1875) of the consequences of starvation in different species. Gull probably knew of Chossat's (1843) monograph, *Recherches expérimentales sur l'inanition*, since it was awarded the Montyon Prix in experimental physiology by the Académie des Sciences de Paris. In that work, Chossat described the results of 13 experiments in which he warmed a total of 26 different animals (17 turtledoves, 7 pigeons, 1 hen, and 1 guinea pig) after he had deprived them of food to the point of impending death. Chossat (1843, p. 630) claimed that his experiments with heat had been performed "dans le but de découvrir ce qui se passe, et non dans celui de guérir des animaux inanitiés" (with the aim of discovering what happens, and not in order to cure emaciated animals; translation by present authors). Nevertheless, Gull appears to have used this research to justify the recommendation that patients be supplied with heat. Since Gull did not provide any further rationale for the use of heat, we can only guess that his recommendation was based on clinical experience of the facilitatory role of heat in increasing food intake in his patients.

SUMMARY

Previous research on weight loss produced by the combination of restricted feeding and unrestricted access to a running wheel has been carried out by using wide variations in AT with only very limited attempts to examine directly the effect of this variable. Research is needed to clarify the effects of AT on the main dependent variables used in activity-based anorexia research—namely, spontaneous running, food intake, and body weight. The possibility that excessive activity and weight loss interfere with the regulation of body temperature provides a new perspective for research on the modulating role of AT. It appears that high ATs promote longer survival and reduce activity. Furthermore, the reduction in activity seems to allow rats to improve their meal efficiency, either preventing or counteracting activity-induced suppression of eating. In addition to this effect on feeding, a high AT could have a direct facilitatory role on feeding in rats that have already met the criterion of 25% of weight loss. The possibility that high ATs provide sustained protection against weight loss needs to be examined in order to obtain a better understanding of self-starvation in the rat produced by the activity-based anorexia procedure. Finally, in an intriguing echo of a suggestion made in the first clinical report to identify anorexia nervosa, the potential of high AT for reversing activity-based anorexia could be important for a therapeutic extrapolation to human anorexia.

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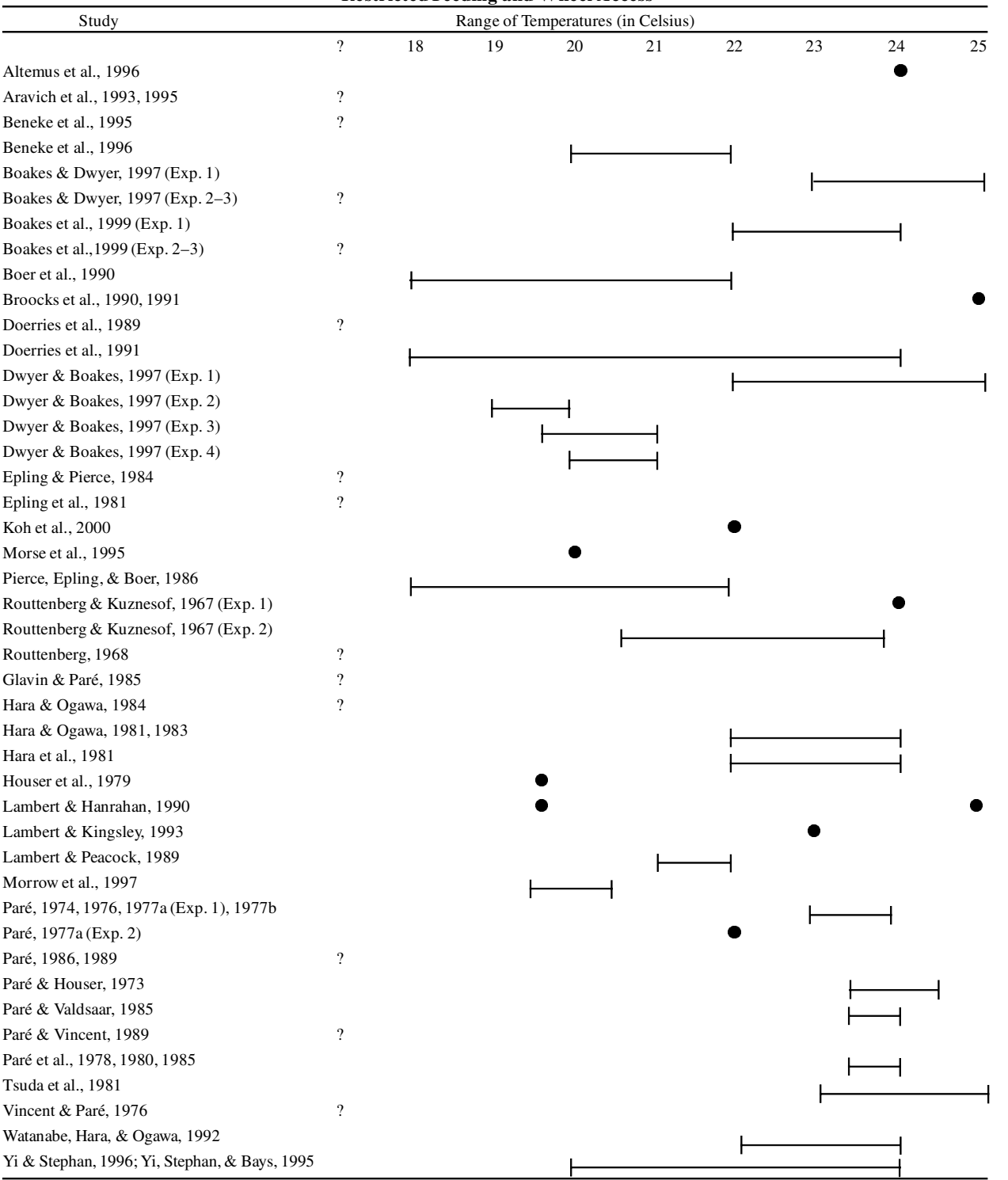
APPENDIX

Visual Representation of the Diversity of Ambient Temperatures Employed in Studies Combining Restricted Feeding and Wheel Access



Note—?, ambient temperature not reported.

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