course of resynchronization of the circadian activity rhythm after a phase shift of the Zeitgeber cycle. These effects can hardly be referred to as after-effects of short and long photoperiods on the circadian period as described by Pittendrigh and Daan[8] because in both species the period length of the free-running circadian activity rhythm varies only within a very narrow range[3]. Both the reduced speed of resynchronization and the occurrence of antidromic resynchronization point to the fact that 24-h LD cycles with a prolonged D-phase possess a lower Zeitgeber strength for the circadian system of nocturnal species than LD's with L- and D-phases equal in duration. We assume that this generally holds true and that light-active species would react in a way analogous to the nocturnal species tested, if the duration of the L-phase of an 24-h LD cycle exceeds 12 h. In this respect also human beings - in whom LD cycles are not fully ineffectual, despite the fact that social factors are the principle Zeitgeber[9] - should be tested to see whether the time needed for resynchronization after transmeridian flights at higher latitudes is larger in summer than during the equinoxes, and whether a pronounced temporary internal desynchronization of circadian functions[10] can occur as a result of the lower Zeitgeber strength of the natural illumination cycle with a greater day length.

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Fever and survival in the rat. The effect of enhancing the cold defence response

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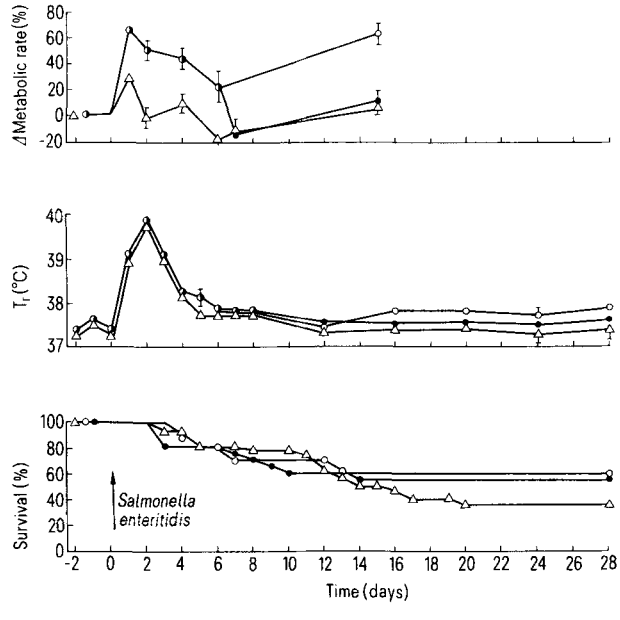
Summary. Continuous cooling of the spinal cord for 6 and 28 days had a probably beneficial effect on the outcome of salmonellosis in the rat, suggesting that the apparently harmful effect of high fevers is not due to the cold defence response but may rather be caused by the high body temperature.

The febrile response of a mammal may be a defence against invading microorganisms[2]. However, the enhancement of the normal febrile response of rats by cooling their preoptic areas increases mortality from salmonellosis[3]. High fevers, furthermore, are associated with increased mortality in both humans[4] and rabbits[5]. This effect could be caused by the febrile activation of any of the cold defence responses - the increase in metabolic rate is thought to be particularly detrimental[6,7] - or by the high body temperature. To investigate the former possibility, I cooled the cervical spinal cord of rats infected with *Salmonella enteritidis*. Spinal cord cooling enhances the cold defence responses but has no effect on body temperature in the rat because the rise in heat production so induced equals the amount of heat lost to the thermode[8,9]. This methode of enhancing the cold defence responses seemed preferable to cold exposure, for cold exposure cools the peripheral tissues and, in infected rats, it usually induces hypothermia[10].

Materials and methods. Spinal cord thermodes were chronically implanted in 130 specific pathogen free, male Wistar rats under pentobarbital anesthesia. The animals, weighing about 350 g at the time of operation, were then fixed to an antirotatory device[3] that allowed freedom of movement otherwise, and caged individually in a room at 23 °C with natural illumination. Food and water were continuously available. 3 weeks after the implantation, 60 animals that showed no apparent signs of spinal compression were i.p. infected with 1 ml of a suspension of live *S. enteritidis*[3] containing 0.002 mg bacterial dry weight/ml. In 30 randomly chosen control animals, the disease was allowed to follow its natural course, while in the other animals the spinal cord was continuously cooled with water at 23 °C starting shortly after the induction of the infection. In 20 of



Average changes in metabolic rate and body temperature, and survival in rats infected with live *S. enteritidis*. In the control (△) and in the experimental animals, the pathogen was injected on day zero and the spinal cord of the experimental animals was then continuously cooled for 6 (●) or 28 (○) days. Note that in the first 6 post-infection days, the temperature and metabolic data for both groups of experimental animals were pooled because they were treated the same, and that after the 1 infection day the metabolic rate was determined in only 8 control and 8 experimental animals. The standard errors (vertical lines) are shown only when larger than the symbols.

these animals, the spinal cord was cooled for 6 days, about the normal duration of the febrile response, whereas in the other 10 the spinal cord was cooled for 28 days, the maximal duration of the disease. Body temperature was daily measured at noon with a thermocouple inserted about 60 mm beyond the anus. Oxygen consumption was determined, as required, by an open circuit method[3]. At various times of the day, but in each animal always at the same hour, the animals were placed in a metabolic cage; 30 min were allowed for the animals to quiet down and resting oxygen consumption was then determined for a further period of 30 min.

Results and discussion. In the days preceeding the infection, the body temperature of all animals averaged 37.5 ± 0.1 (SE)°C and the metabolic rate 7.6 ± 0.2 ml O_2/min. Cooling the spinal cord induced in the experimental animals a steady state increase in metabolic rate of $60.5 \pm 5.3\%$ ($p < 0.001$) but had no significant effect on body temperature.

The figure summarizes the results of the infection. The metabolic rate of the control animals increased by $28.6 \pm 3.5\%$ ($p < 0.001$) during the chill phase of fever and then it slowly decreased, being depressed by nearly 20% at the end of the febrile period. The metabolic rate of the experimental animals paralleled these changes at a higher level ($p < 0.001$) but it reached a maximum of only $66.1 \pm 4.8\%$ during the chill phase of fever. This suggests that the effects of fever and spinal cord cooling on heat production are not additive, probably because the thermosensitivity of the spinal cord, like that of the preoptic area[11], is reduced during fever. Despite this higher rate of heat production, the experimental and control animals had the same febrile temperatures. The survival of the experimental animals, however, exceeded that of the controls in each of the 5 independent series of experiments done and this effect was probably significant ($p = 0.06$, sets of contingency tables[12]).

These experiments thus show that the thermoregulatory increase in metabolic rate, which is considered detrimental for febrile patients because it increases the work of the heart and leads to the loss of weight, nitrogen and fluids[7], had no harmful effect on survival. Consequently, the detrimental effect of enhancing the febrile response by cooling the preoptic area[3] must be due either to some specific response elicited by cooling this region or, perhaps more likely, to the concomitant increase in body temperature - in cell cultures thermal injury may occur even at normal body temperatures[13] and high body temperatures are thought to inhibit various immunological responses[14].

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Blockade of nicotinic receptors in brain with d-tubocurarine induces decreased metabolism, cutaneous vasodilation and hypothermia in rats[1]

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Summary. Direct administration of d-tubocurarine into the lateral cerebral ventricle of conscious rats produced decreased metabolism, cutaneous vasodilatation and hypothermia at ambient temperatures of 8-22 °C. Also, pretreatment with d-tubocurarine antagonized the arecoline-induced hypothermia.

It has been repeatedly documented that intracranial administration of cholinomimetic drugs produces hypothermia in the rat[2-7]. This hypothermia can be antagonized by blockade of central muscarinic receptors with atropine sulfate[7]. The present study assessed the effects of blockade of central nicotinic receptors with d-tubocurarine on thermoregulatory responses and on the hypothermia induced by the cholinomimetic drug arecoline.

Materials and methods. Adult male Sprague-Dawley rats, weighing between 250 and 300 g, were used. The experiments were performed on unanesthetized animals restrained in rat stocks between 9.00 a.m. and 5.00 p.m. Between experiments the animals were housed individually in wire-mesh cages in a room at 25 ± 1.0 °C with a 12-h light-dark cycle. The animals were given free access to tap water and granular chicken feed. For the intracerebroventricular (i.c.v.) injection, a cerebroventricular cannula was implanted in each animal under general anesthesia (sodium pentobarbital, 6 mg/100 g, i.p.), the tip being located at the DeGroot[8] coordinates: AP, 7.0; L, 1.0; and 0.1 mm. A 27-gauge needle was connected via PE 10 tubing to a 50-µl Hamilton syringe. During the surgery the correct positioning of each guide tube was verified by the rapid flow of saline into the lateral cerebral ventricle under gravity. A period of 2 weeks was allowed to permit the animals to recover from the operation. The effects of d-tubocurarine (Sigma, 0.5-2.0 µg) and arecoline (Sigma, 50-200 µg) on metabolic, respiratory and vasomotor functions as well as body temperatures were assessed in a small animal partitional calorimeter[7,9-11]. Metabolic rate (M) was calculated from the animal's oxygen consumption and expressed as watts/kg body weight. Respiratory evaporative heat loss