The effect of environment on the response to injury in the rat

H. B. Stoner

M.R.C. Toxicology Research Unit, Carshalton, Surrey

Summary
Recent work on the effect of changes in the environmental temperature on the local and general response to injury is discussed.

Both the acute and delayed responses to injury are affected by changes in environmental temperature.

Thermoregulation in the rat is impaired by an injury and there is an optimum temperature for survival after the injury.

The acute response to injury in the rat is also affected by the animal’s previous environmental history.

The increased sensitivity to catecholamines produced by cold acclimation alters some of the initial responses.

Introduction
Environmental factors exert a profound effect on the response to injury in the rat, as they do on that in other small mammals. The main environmental factor concerned is temperature and this can affect the response in a number of ways. The growing interest in the effect of changes in ambient temperature on the behaviour of patients suffering from various forms of trauma, such as burns (Barr et al., 1968) and fractures (Cuthbertson, Smith & Tilstone, 1968), makes discussion of these effects desirable. The experimental work to be described has been performed on the rat whose responses are typical of those of other small mammals. In some cases the conclusions drawn from these experiments can be readily extended to man. In other cases their implications for injured man require further study.

Effect of environmental temperature on the injury

The simplest experimental situation is when the rat is exposed to different environmental temperatures both during the period of injury and subsequently. In this situation, raising the ambient temperature in the range 10–37°C increases the mortality rate and shortens the survival time (Haist, 1960; Stoner, 1961). Here the dominant effect is on the size of the injury. Increasing the temperature of the damaged part increases the severity of the damage and consequent fluid loss into the area. This was well shown in the case of burns by Courtice (1946).

The precise mechanism of this effect has not been completely worked out. Local circulatory arrest occurs in most injuries and the lower the temperature the longer the cells can withstand anoxia. Similarly, a low tissue-temperature at the site of the injury will inhibit the activity of those catabolic enzymes which are triggered off by the trauma and which will continue the process of tissue destruction. This is the reasoning behind the use of local and general hypothermia in the treatment of injuries.

At a later stage the environmental temperature can affect the rate of healing of surface wounds. Both burns and surgical wounds of the skin heal faster in a 30°C environment than in a 20°C one [see Cuthbertson & Tilstone (1967) for relevant references]. This has recently been demonstrated for the healing of excised areas of skin in the rat by Cuthbertson & Tilstone (1967) who attributed it to a higher temperature and better circulation in the wound.

Effect of environmental temperature on the response to injury

When rats are injured at an ordinary room temperature of about 20°C the injury is rapidly followed by a fall in deep body (core) temperature. Using gradient-layer calorimeters it has been shown that this is due to a decrease in the rate of heat production (Stoner & Pullar, 1963; Miksche & Caldwell, 1968). Except after haemorrhage this is not due, in the early stages, to a failure of O₂ transport to the heat-producing organs (Tabor & Rosenthal, 1947). (It is important here to distinguish between the early and late stages of the response to fatal injury. In the late stages leading to death the picture is dominated by a failure of O₂ transport. This section is solely concerned with the early part of the response to trauma.) More detailed study of the effect of injuries, such as limb ischaemia and burns, on the core temperature showed that the rate of fall depended on the environmental temperature (Tabor & Rosenthal, 1947; Stoner, 1958; Haist, 1960; Stoner, 1968). If, after a standard injury, the rats were placed in a thermoneutral environment (30–33°C) the core temperature did not fall and even rose. At lower
environmental temperatures the rate of fall appeared to be inversely proportional to the ambient temperature. The rats were unable to meet the demands of their environment and maintain their body temperatures. After non-fatal injuries this disability persisted for 16–48 hr (Tabor & Rosenthal, 1947; Stoner, 1968). Even after injuries which caused little depression of body temperature in a 20°C environment, exposure to air at 3°C caused a prompt fall in core temperature. This inability to produce heat when external conditions required it suggested that injury impaired thermoregulation in the rat and consequently the effect of standard injuries on $O_2$ consumption at different environmental temperatures was studied (Stoner, 1969).

$O_2$ consumption is minimal when the rat is in a thermoneutral environment (see Gelineo, 1964). As the environmental temperature is lowered below the critical temperature of 30°C, $O_2$ consumption increases to maintain body temperature in the face of the increasing temperature gradient between the rat and its environment. Rats were injured either by 2 or 4 hr bilateral hind-limb ischaemia in a 20°C environment or by scalding the dorsum with water at 83°C for 30 sec to give a full thickness burn of 20% of the skin surface and keeping them at 20°C for 2.5 hr afterwards. After these standard injuries the $O_2$ consumption of the rat was measured at different environmental temperatures between 10° and 33°C.

In the thermoneutral zone it was found that $O_2$ consumption was not inhibited by these forms of trauma unless the injury proved fatal and even then $O_2$ consumption was maintained at the normal rate until just before death. Trauma lowered the critical temperature, the depression increasing with the severity of the injury. Within this new, extended thermoneutral range the $O_2$ consumption of the injured rat fell to the basal rate and remained there, only declining further in the terminal stages. At environmental temperatures below the new critical temperature, trauma inhibited $O_2$ consumption in such a way that the regression line for $O_2$ consumption on environmental temperature was moved to the left without altering the slope, the separation from the controls depending on the severity of the injury. In other words, in the early part of the response injury inhibits the thermoregulatory part of $O_2$ consumption.

Further work is now required to elucidate the mechanism of this important effect of injury in the rat. Which part of the thermoregulatory system is impaired by trauma? This question cannot be answered yet. The effect produced by trauma does not correspond to any well-known situation. Some possibilities can be excluded. Non-specific interference with heat production, such as by failure of $O_2$ transport, should have caused most effect at 30°C when cardiovascular function is more severely affected. A toxic factor from the damaged tissue inhibiting oxidation could also be expected to be liberated as well at 30°C as at 20°C. The parts of the system which seem most suitable for further study are the centres in the hypothalamus and the efferent control pathways with their effector mechanisms. When one has some appreciation of the mechanisms involved in the rat one will be more able to relate these findings to man.

Effect of environmental temperature on survival after a standard injury

A further effect of environmental temperature on the response to injury must be considered. When rats are given the same injury under standard conditions, for example a period of bilateral hind-limb ischaemia in a 20°C environment, and then exposed to different ambient temperatures it is found that there is an optimum temperature for survival (Tabor & Rosenthal, 1947; Green & Stoner, 1950; Haist, 1960). This phenomenon is common to all types of injury in the small mammal. The actual temperature seems to vary somewhat with species and in the rat is about 20–22°C. On either side of this optimum temperature the mortality rate increases and the survival time shortens after the standard injury. It is important to realize that the optimum temperature is below the thermoneutral range and that under these conditions the core temperature will fall several degrees. From a teleological standpoint the optimum environmental temperature is one which allows the body temperature to fall at an optimum rate to a level which is not so low that unaided recovery is impossible yet which confers advantages by limiting the injury and husbanding the body's metabolic resources.

Like so much in this field this phenomenon cannot be fully explained. It is, perhaps, the result of the interaction of the two effects of changes in environmental temperature discussed above. A low ambient temperature will decrease the local effect of the injury but increase the fall in body temperature whereas a high ambient temperature will have the opposite effects. At some intermediate point the influence on the local and general effects of the injury may be such that recovery is favoured.

Effect of previous environmental history on the response to injury

So far we have considered the effect of acute changes in environmental temperature on the response to injury in rats which had been reared since weaning at an ambient temperature of 18–22°C. Haist (1960) found that if rats were cold-acclimated (Hart, 1961) by exposure to low environmental temperatures (<5°C) before being injured in a 20°C
environment they responded differently from similarly injured conventional rats. There were two main differences. Firstly, the cold-acclimated rats were apparently more resistant to limb ischaemia, showing a lower mortality rate and a longer survival time in fatal cases. Secondly, the rate of fall in \( \text{O}_2 \) consumption and core temperature after the injury was slower in the cold-acclimated rats.

Further study of these phenomena (Stoner, 1965) showed that the apparent increase in resistance to limb ischaemia was only seen in rats exposed to low temperatures (3°C) for long periods (50–106 days). These intervals are much longer than the 14–21 days required for full cold-acclimation in the rat. The apparent increase in resistance was only found if they had been in a cold environment sufficiently long for the altered pattern of growth in the cold to lead to anatomical changes which reduced the proportional size of the hind-quarters. These cold-acclimated rats were not actually more resistant; they appeared to be because the size of the injury to the hind-limbs was reduced.

On the other hand the changes in the rate of fall of core temperature and \( \text{O}_2 \) consumption were seen as soon as the rats were fully acclimated to cold, after 14–21 days, and the differences from conventional rats were also seen after thermal injury (Stoner, 1968). Under these conditions the size of injuries was the same as in the conventional rats. These differences are attributed to the greater sensitivity of cold-acclimated rats to the thermogenic action of catecholamines (Stoner, 1965; Stoner & Westerholm, 1969; Stoner & Little, 1969).

**Effect of environmental temperature on traumatic fever**

Except for the remarks on wound healing all the observations above refer to the effect of environmental changes on the acute response to injury, that is what Cuthbertson (1942) has called the ‘ebb’ phase. In animals which recover this is followed by another phase called by him the ‘flow’ phase. Characteristics of this phase are excessive protein breakdown and an increase in heat production with a rise in core temperature (traumatic fever). The increase in heat production is thought to come from the oxidation of protein.

The effect of variations in the environment on this phenomenon has recently been studied in several centres. Work on this topic arose from studies on the environment of burns patients. It was found, both in man and animals, that raising the environmental temperature to 30°C during the period of hypercatabolism after burns greatly reduced the increase in \( \text{O}_2 \) consumption, etc. (Caldwell et al., 1959; Caldwell, 1962; Caldwell, Hammel & Dolan, 1966; Barr et al., 1968). At this stage after burning there is a large increase in the evaporative loss of water from the body, even in animals like the rat where the skin does not blister. The latent heat of evaporation for this water had to be met by the body and it was thought the consequent increase in heat production accounted for the rise in \( \text{O}_2 \) consumption seen at this time (Moyer, 1962; Roe, Kinney & Blair, 1964; Harrison et al., 1964). Raising the environmental temperature to 30°C would reduce the thermal gradient between the body and its surroundings and spare heat for this purpose.

Following this work there was a tendency to consider the increased heat production during recovery from injury at environmental temperatures below thermoneutrality as a response to an increased evaporative loss of water from the body. While this may be a considerable part of the explanation after burns it is not the whole explanation. Raising the environmental temperature to 30°C also decreases the catabolic response and increased heat production after fractures in both man and rats and under these conditions there is no increased evaporative loss of water (Campbell & Cuthbertson, 1966, 1967; Miksch & Caldwell, 1967; Cuthbertson et al., 1968).

At present an explanation is lacking both for the delayed increase in metabolic rate after injury and for the effect of changes in environmental temperature on this response.

**Conclusions**

Environmental changes can clearly influence all stages of the response to injury in the rat. Except perhaps for their effect on the local damage produced by the injury and on certain aspects of the delayed response to burns the influence of environmental changes cannot be satisfactorily explained. The necessity for further work is emphasized by the growing clinical interest in this subject.

**References**


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