The therapeutic potential of regulated hypothermia

Christopher J Gordon

Abstract

Reducing body temperature of rodents has been found to improve their survival to ischaemia, hypoxia, chemical toxicants, and many other types of insults. Larger species, including humans, may also benefit from a lower body temperature when recovering from CNS ischaemia and other traumatic insults. Rodents subjected to these insults undergo a regulated hypothermic response (that is, decrease in set point temperature) characterised by preference for cooler ambient temperatures, peripheral vasodilatation, and reduced metabolic rate. However, forced hypothermia (that is, body temperature forced below set point) is the only method used in the study and treatment of human pathological insults. The therapeutic efficacy of the hypothermic treatment is likely to be influenced by the nature of the reduction in body temperature (that is, forced versus regulated). Homeostatic mechanisms counter forced reductions in body temperature resulting in physiological stress and decreased efficacy of the hypothermic treatment. On the other hand, regulated hypothermia would seem to be the best means of achieving a therapeutic benefit because thermal homeostatic systems mediate a controlled reduction in core temperature.

(*Emerg Med J* 2001;**18**:81–89)

Keywords: temperature regulation; chemical toxicants; ischaemia; stroke

There has been a resurgence in the use of hypothermia as a means of reducing or blocking the pathological damage resulting from traumatic brain injury, ischaemia in the CNS, and insults to other organs.[1–6] Although the mechanisms of action of hypothermic protection are not entirely understood, it seems clear that a lower temperature protects tissues deprived of oxygen by slowing the rate of cellular damage that occurs from formation of free radicals, chemical metabolites, and tissue oedema. In addition to protection from ischaemic damage, hypothermia has been shown to ameliorate the toxicity of various drugs and environmental toxicants as well as protect from other insults such as haemorrhage, hypergravity, and hypoglycaemia.[7]

A major problem with using hypothermia as a treatment is that body temperature is forced below the normal level dictated by the set point temperature. This will result in a myriad of physiological responses that would counter the therapeutic benefits of the hypothermic treatment. The thermoregulatory system of homeotherms (that is, most birds and mammals) responds quickly to a reduction in internal temperature with vigorous heat gain and conserving responses to counter the loss in body heat. This not only reduces the efficacy of the methods used to induce hypothermia but, more importantly, creates undue physiological and psychological stress and may counter the benefits of the hypothermic treatment.

Regulated or controlled reductions in body temperature via a reduction in the set point seem to be a much better method of achieving a hypothermic state. It seems that the set point temperature of laboratory rodents is reduced when they are subjected to insults such as exposure to toxic chemicals and hypoxia and there is a resulting regulated reduction in body temperature.[7 8] It follows that regulated hypothermia could also be a useful approach to lower body temperature of larger species, including humans, subjected to insults. Of course, there are many problems to overcome when extrapolating the thermoregulatory responses from rodents to humans. The goal of this paper is to propose that regulated rather than forced reductions in body temperature should be considered in the future use and study of therapeutic hypothermic treatment.

Neural mechanisms of thermoregulation

Thermoregulation in mammals and other species is complex, involving many levels of control and interaction with other physiological processes in the central and peripheral nervous systems. For details on the thermoregulatory system, the reader is referred to recent reviews.[7 9 10] To understand the thesis to be presented in this paper, it is necessary to explain the thermoregulatory control processes in terms of a relatively simple, negative feedback loop (fig 1). This regulatory scheme is widely used by thermal physiologists to explain most thermoregulatory phenomena. The main function of the thermoregulatory system is to maintain a stable temperature of the internal tissues and organs (that is, core). A stable core temperature is achieved while allowing temperature of the shell (skin and peripheral tissues) to vary with that of the ambient temperature (T_a). The preoptic area and anterior hypothalamus (POAH) is considered a key site for integration and central processing of thermoregulatory signals (fig 1). Warm and cold thermoreceptors in the skin and core convey temperature information to the POAH and other sites in the CNS. A set point or reference temperature, thought to be

Neurotoxicology Division, National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, Research Triangle Park, North Carolina 27711, USA

Correspondence to: Dr Gordon (gordon.christopher@epa.gov)

Accepted 26 April 2000

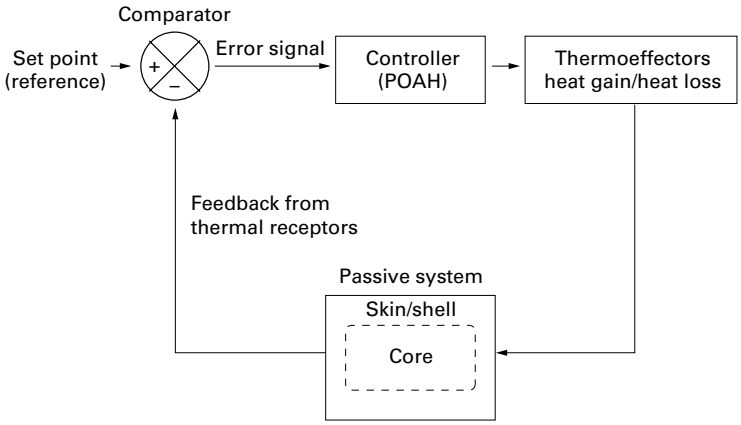

Figure 1 Basic model of thermoregulatory control system using the concept of a servo, negative feedback with proportional control. Model adapted from Stolwijk and Hardy.[70]

generated by a network of warm, cold, and thermal insensitive neurons in the POAH,[10 11] is compared with feedback from the thermoreceptors in the skin and core. An error signal that is proportional to the difference between the set point and feedback signal is generated. The error signal activates the appropriate thermoeffector pathways that control heat production and heat loss. The scheme of negative feedback, proportional control explains how the thermoregulatory system achieves a balance between heat production and heat loss resulting in a stable core temperature.

The concept of single set point temperature is extremely useful for explaining many thermoregulatory phenomena in homeothermic and poikilothermic species. Thermal physiologists define set point as "The value of the regulated variable found in the condition when external or internal interferences tending to alter the regulated variable, and the resulting effector activities tending to counteract these alterations, are both minimal".[12] In other words, if an organism uses its thermoeffectors to maintain core temperature at 37.5°C then it is assumed that its set point or reference temperature is set at 37.5°C. The circadian rhythm of core temperature is thought to reflect a 24 hour oscillation in the set point temperature. The concept of the set point temperature is generally accepted by thermal physiologists. However, it should be noted that the existence and operation of a set point temperature is questioned by some researchers.[9 13] That is, the engineering analogy of a set point can be misleading in the interpretation of some complex thermoregulatory responses. None the less, the set point concept is useful to explain many of the thermoregulatory processes in the discussion that follows.

Whether or not set point has changed when body temperature changes in response to an environmental or chemical challenge has been the focus of many studies.[7 9 14] The set point theory is based on the premise that the thermoregulatory system operates continuously to maintain core temperature (T_c) equal to set point temperature (T_{set}) (table 1). Under baseline conditions, T_{set} is equal to T_c and there is a balance between activation of heat gain and heat loss thermoeffectors. A change in T_{set} leads to marked changes in the thermoregulatory response. Fever from infection is the corner stone of a set point increase[15] and is also termed regulated hyperthermia.[7 8] During infection, cytokines released into the circulation activate thermoregulatory neurons in the POAH causing an abrupt increase in T_{set}. When $T_{set}>T_c$, there is an activation of thermoeffectors to increase heat production (for example, shivering and non-shivering thermogenesis) and reduce heat loss (for example, peripheral vasoconstriction; seeking warm environment) that eventually leads to an equalling of T_{set} and T_c but at an increased body temperature. On the other hand, during forced hyperthermia, T_c increases above T_{set} as would occur by exposure to high ambient temperatures. There is an activation of thermoeffectors to reduce heat gain and increase heat loss to lower body temperature. Forced hypothermia refers to the state when T_c is forced below T_{set}, as would occur during acute cold exposure or treatment with drugs that impair thermogenesis. The organism responds with an activation of thermoeffectors to reduce heat loss and increase heat gain.[7 8] Regulated hypothermia is the least understood of the thermoregulatory responses. It occurs when internal and/or external factors reduce T_{set} below T_c. The organism responds by activating thermoeffectors to increase heat loss and reduce heat production. These responses persist until T_c is equal to T_{set} but at a lower body temperature. Anapyrexia, a term to describe the recovery of body temperature from a febrile state, is also considered a form of regulated hypothermia. To sum up the hypothermic responses, a reduction in set point mediates a controlled reduction in body temperature where behavioural and autonomic thermoeffectors participate to dissipate body heat and achieve a hypothermic body temperature. Any attempt of forced hypothermia in a homeotherm is met by a vigorous response of thermoeffectors to increase heat production and reduce heat loss to prevent body temperature from falling.

Table 1 General changes in activity of autonomic and behavioural thermoeffectors of a homeotherm when subjected to forced or regulated changes in core temperature (T_c). T_{set} = set point temperature

		Thermoeffector response			
Thermoregulatory state		*HP*	*SBF*	*EHL*	*ST_a*
Normothermia	[$T_c=T_{set}$]	◆	◆	◆	◆
Forced hyperthermia	[$T_c>T_{set}$]	▼	▲	▲	▼
Regulated hyperthermia	[$T_{set}>T_c$]	▲	▼	▼	▲
Forced hypothermia	[$T_c<T_{set}$]	▲	▼	▲	▲
Regulated hypothermia	[$T_{set}<T_c$]	▼	▲	▼	▼

HP = heat production; SBF = skin blood flow; EHL = evaporative heat loss; ST_a = selected ambient temperature; ◆ = baseline responses; ▲ = increase; ▼ = decrease.

Therapeutic benefits of hypothermia

Depending on the species of mammal, a stable core temperature of 36 to 39°C is maintained throughout most of its life. A stable core temperature is equated with optimal health. Any prolonged deviation in the normal core temperature is generally considered to be a sign of disease or other pathological condition. On

Table 2 General thermoregulatory effects of acute insults in laboratory mammals including mouse, rat, and/or rabbit. Literature in table cited in Gordon[25 31] except where noted

	Thermoeffector response			
Insult	*HP*	T_s	ST_a	T_c
Chemical toxicants				
Ni, Cd, Se		?		
DFP		▲		
chlorpyrifos*	?	?		
ethanol		▲		
ozone		?	?	
Biological toxins				
LPS endotoxaemia†	?	▲		
bee and cobra venom		?	?	
brevetoxin‡	?	?		
Pathophysiological insults				
hypoglycaemia		?	?	
hypoxia		▲		
uraemia		▲		
skin burn		?	?	
hypovolemic shock§			?	
vascular ligation		?	?	
hypergravity		▲	?	

▼ = reduction; ▲ = increase; HP = heat production; T_s = skin temperature; ST_a = selected ambient temperature; T_c = core temperature. Additional references; *Gordon[47]; †Romanovosky *et al*[71]; ‡Gordon (unpublished); §Henderson *et al*[72]. DFP = diisopropyl fluorophosphate; LPS = lipopolysaccharide.

the other hand, it is well known that moderate reductions in body temperature improve the ability of rodents and other laboratory mammals to survive a variety of pathological insults (table 2). Research has focused on the mechanisms by which reduced temperature improves the recovery to insult. In addition, there has been a resurgence in determining how the thermoregulatory system responds when the animal is subjected to various insults. Hypothermia improves survival to many insults; however, for sake of space, this paper will focus on just two well studied insults: hypoxia/ischaemia and chemical/drug toxicity.

HYPOXIC/ISCHAEMIC INSULT

There has been renewed interest to utilise hypothermia as means to protect the brain, heart, and other organs when subjected to hypoxia and/or ischaemia. It has been known for decades that rodents subjected to hypoxia become hypothermic and the hypothermic state prolongs survival in the hypoxic environment. For example, mice subjected to acute hypoxia by exposure to simulated altitudes had a lethal altitude ceiling of 30 000 ft at an ambient temperature of 34°C; lowering ambient temperature to 16°C led to an increase in the lethal altitude ceiling to 48 000 ft.[16] During hypoxia, mice maintained a normal body temperature at a T_a of 34°C but became hypothermic at the cooler T_a temperatures. Hence, by becoming hypothermic in the cool environment, the mouse's survival time to hypoxia was markedly improved.

During parturition, newborns face the potential danger of becoming hypoxic to the point of causing irreversible damage to the CNS. Hence, there has been considerable interest to determine how hypothermia can be utilised to protect newborn animals subjected to hypoxia. Inducing a forced reduction in body temperature in neonates imparts marked protection to the CNS during hypoxia.[17–19] In addition to improved survival, it seems that a reduction in body temperature will protect the adult and neonatal mammal from the general pathological effects of hypoxia and hypoxemia. It is important to note that newborn altricial rodents (for example, rat, mouse, and hamster) are essentially poikilothermic and likely to become hypothermic following parturition into a relatively cool environments (that is, standard room T_a). It is well known that neonatal animals have a much higher tolerance to hypoxia than adults.[20] This higher tolerance to hypoxia may be attributed in part to the neonate's small size and greater thermal lability compared with adults.

Using the rat, mouse, and gerbil as key experimental species, it has been found that a moderate reduction in brain temperature of >2°C affords marked protection to the CNS when subjected to acute ischaemia.[1 2 15] The neuroprotective effect of glutamate antagonists such as MK-801 in mouse and gerbil have been found to be a result of the drug's ability to lower body temperature.[21 22] The efficacy of drugs with supposed anti-hypoxic properties such as adenosine, diazepam, and pentobarbital were found to be associated with their ability to induce hypothermia in mice rather than having any specific protective effects.[23]

While lowering brain temperature provides additional protection to ischaemia, it seems that hyperthermic temperatures worsen the outcome from brain ischaemia.[2] This finding should be a major concern in the treatment of many brain injuries because of the common occurrence of fever in patients with stroke.[24 25] Stroke patients with fevers are considered to be at greater risk to permanent neuronal injury compared with afebrile patients with a stroke.[26] Indeed, Ginsberg and Busto[27] recommended that "...fever be combated assiduously in acute stroke and trauma patients...".

Ischaemic injury in other aerobic organs including heart and kidney are also attenuated by reductions in temperature. Reducing temperature down to 31–35°C provides increased protection to the ischaemic kidney.[28] Hyperthermic core temperatures (about 39°C) augment the damage resulting from renal ischaemia.[29] The ischaemic heart has been found to be very sensitive to the temperature of the perfusate. A 3 to 4°C reduction in the reperfusate of an ischaemic heart will attenuate many symptoms of myocardial dysfunction.[30] Ischaemia-reperfusion injury is the lung is also attenuated with 6–8°C reduction in temperature.[31]

TOXIC CHEMICAL INSULT

The in vitro and in vivo toxicity of many environmental toxicants and drugs is directly proportional to temperature.[7 8 32 33] For example, the LD_{50} dose of chemicals such as ethanol, heavy metals, methylmercury, pesticides, and others is generally reduced as the ambient temperature is increased from the standard room temperature (22°C) to temperatures equal to or exceeding the species' thermoneutral zone.[8] These chemicals induce hypothermia at doses approaching the LD_{50}; however, when ambient temperature is increased to thermoneutrality,

the hypothermic effects abate and the toxicity of the chemical increases.[7 8] Biological endpoints of toxicity other than lethality are also affected by ambient and body temperature in a manner similar to lethality. For example, rates of tumour formation,[34] tissue accumulation of methylmercury,[35] visual dysfunction,[36] and cardiovascular function[37 38] have been shown to increase with rises in body and/or ambient temperature in rodents administered toxic doses of drugs and chemicals.

From 1900 to 1940 there was considerable effort to study the effects of body temperature on drug toxicity using poikilothermic and homeothermic species (reviewed by Furhman[33]). The lethal dose of agents such as digitalis, insulin, tetanus toxin, oxygen at high pressure, and procaine were consistently reduced in species that were maintained in warm environments. The in vitro toxicity of most chemicals also increases with temperature.[39] This synergy between temperature and chemical cytotoxicity has proved to be valuable in the development of more effective chemotherapeutic agents.[40]

MECHANISM OF HYPOTHERMIC PROTECTION

How does a reduced body temperature provide protection? The absorption, distribution, metabolic activation and deactivation, and excretion of a chemical involve biochemical reactions that are temperature dependent. Several mechanisms may be operative to explain how hypothermia is protective (for review, see Coulbourn *et al*[3]). That a reduced temperature will slow the rate of cellular damage regardless of the type of insult is the simplest explanation. The Q_{10} is a useful way of explaining how temperature affects metabolic processes and is defined as the factor by which the rate of a biochemical reaction is increased for a 10°C rise in temperature.[41] Generally, most biological processes fall into a Q_{10} range of approximately 2.5. This means that a 1°C reduction in temperature will lead to a 9.6% reduction in the rate of cellular respiration, oxygen demand, carbon dioxide production, etc. For example, a reduced demand for oxygen during hypothermia is especially critical in highly aerobic organs such as the brain and heart subjected to ischaemia. Reduced temperature slows the rate of lipid peroxidation[42] and protects ischaemic cell membranes by stabilising potassium efflux.[43]

When considering the protective effects of hypothermia on chemical toxicity, there is a reciprocal relation between the magnitude of the toxic effect and the duration by which the drug or chemical will remain in the organism. It seems that the deactivation and excretion of a toxicant will increase with body temperature but the toxicity of the chemical will decrease with a reduction in body temperature.[8 32] Ethanol serves as an ideal example of the trade off between toxicity and metabolism of a chemical as a function of body temperature. Mice dosed acutely with ethanol become hypothermic, a response that enhances their survival.[44] The hypothermic state depresses metabolism and slows the rate of detoxification of ethanol resulting in higher circulating levels of ethanol lasting for longer periods of time.[45] When body temperature is normal, the ethanol is cleared faster but the mice have a reduced survival.

Natural forms of regulated hypothermia

It is clear that a variety of insults cause marked reductions in body temperature of rodents. In view of the correlation between hypothermia and increased survival to the insults, it is reasonable to postulate that the hypothermic response to the insults is adaptive and likely to be regulated. This laboratory and others used behavioural thermoregulation as a means of understanding whether or not rodents subjected to insults underwent forced or regulated reduction in body temperature. It was found that mice and rats allowed to behaviourally thermoregulate in a temperature gradient selected cooler ambient temperatures at the same time as body temperature decreased from the insult.[7 8 46] Insults such as acute exposure to metals (for example, nickel, cadmium, selenium, lead) (for review, see Gordon[7] and Gordon *et al*[8]), organophosphate pesticides,[47 54] ethanol,[47] hypoxia,[48 49] endotoxaemia[52] and uraemia[53]were shown to induce a preference for cooler ambient temperatures and reduced body temperature (table 2). For example, the rat housed in a temperature gradient and exposed to 6.9% oxygen for 6.5 hours quickly developed a hypothermic core temperature from 37 to 34.5°C. The hypothermic response was accompanied with a reduction in the preferred ambient temperature from 30 to 24°C and a 50–75 beat/min increase in heart rate (fig 2). Replacing hypoxic air with normoxic air resulted in an increase in selected ambient temperature and rapid recovery to a normothermic core temperatures. The hypoxic atmosphere also causes a transient increase in dry heat loss and reduction in CO_2 production, reflecting peripheral vasodilatation and reduced metabolism during the initial stages of hypoxia.[51] Thus, the hypoxic rat seems to modulate both behavioural and autonomic thermoeffectors to mediated a regulated reduction in body temperature and could maintain this hypothermic state for at least six hours of hypoxia. This laboratory has also shown that rats exposed to organophosphate pesticides will maintain a similar state of regulated hypothermia for at least four hours.[47 54]

In general, rodents subjected to hypoxic and toxic chemical insults never select warm ambient temperatures to prevent a reduction in core temperature. If the insult caused a forced reduction in body temperature, one would expect a preference for warmer ambient temperature. Because animals exposed to the insults selected cooler ambient temperatures and maintained a hypothermic state, it is concluded that the set point for control of body temperature is reduced after exposure to the insult. There is little evidence that humans exhibit these thermoregulatory responses. This is most probably attributed to differences in body mass as well as other physiological differences (see later).

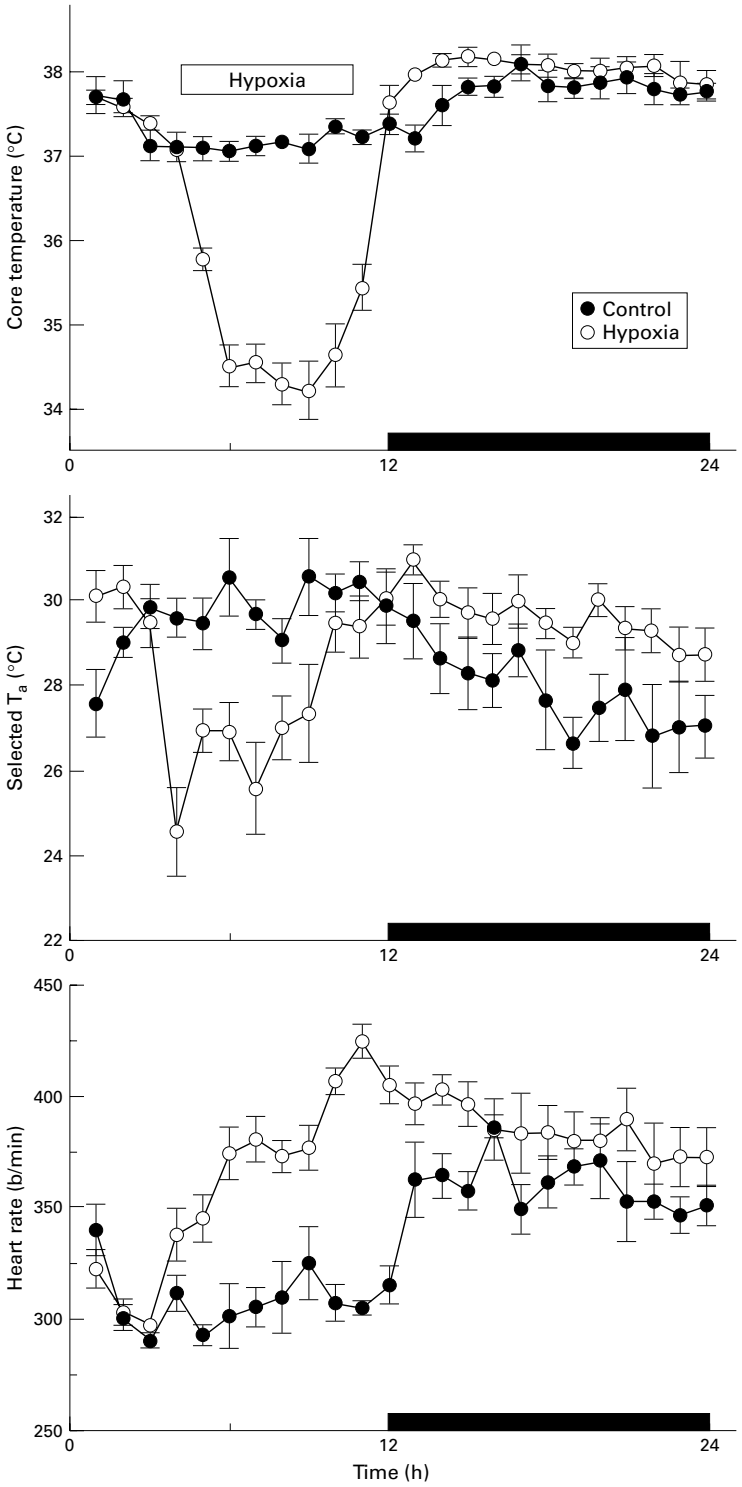

Figure 2 Example of regulated hypothermic response to hypoxia. Core temperature, heart rate, and selected T_a were monitored by radiotelemetry from six rats allowed to behaviourally thermoregulate in a temperature gradient. Hypoxic air (6.9% oxygen) was pushed into gradient for 6.5 hours. Note preference for cooler T_as occurs during onset of hypoxia before core temperature decreases. Black bar indicates dark phase. Rats were adapted to gradient for several days before hypoxia. Data modified from Gordon.[51]

Regulated versus forced hypothermia: consequences to pathophysiology

Pathophysiologists must be aware that rodents subjected to a variety of insults undergo regulated and not forced hypothermia. This should have a tremendous impact on the design of a multitude of physiological, toxicological, and pharmacological studies. To this end, there are three major issues that should be considered: (1) Is forced or regulated hypothermia a better means of studying and possibly treating these pathological insults? (2) Can the benefits of regulated hypothermia observed in laboratory rodents be extrapolated to species such as humans? (3) How can our understanding of regulated hypothermia be used in the design of future studies? These issues are explained below.

BENEFITS OF REGULATED HYPOTHERMIA

Forcing body temperature below its regulated level will evoke different physiological responses compared with a regulated reduction in temperature. The manner in which temperature is reduced will have marked impacts on the animal's health and general physiological state. Forcing body temperature below the set point temperature results in an immediate response to increase heat production and reduce heat loss. The greater the decrease in body temperature, the greater the increase in the error signal in the POAH comparator, resulting in more vigorous thermoeffector responses to increase body temperature (see fig 1). In addition to the activation of thermoeffectors directly involved to reduce heat loss and increase heat production, other physiological effects of cold stress would also ensue during forced hypothermia. From a clinical perspective, these physiological responses would be considered undesirable and would complicate a clinical treatment. For example, activation of the thyroid and adrenal systems (for example, increase in circulating corticosteroids), altered immune response, lipid hydrolysis and mobilisation of free fatty acids, alterations in glucoregulation, tachycardia, tachypnea, and altered renal, hepatic, and gastrointestinal function would occur during forced hypothermia.[55]

Clinical methods of forced hypothermia are often used in the treatment of malignant hyperthermia and induction of hypothermic states for surgery.[56] Some attempts have been made to use forced hypothermia to treat brain injuries.[57] The procedures of forced hypothermia include ice water immersion, contact with a cold mattress, and lavage of cold fluids. In all cases, the subjects encounter discomfort and activate thermoregulatory responses to raise heat production and reduce heat loss. Cold water immersion often has an undesirable "afterdrop" in core temperature of about 2°C that results from the redistribution of body heat during recovery from the ice water immersion.[58]

The methods of forced hypothermia are all likely to impart a stressful response that may be avoided by utilising regulated hypothermia. Reducing the core temperature using conventional methods of forced hypothermia is analogous to slowing an automobile by applying pressure to the brake while continuing to maintain the speed of the automobile by sustaining pressure on the acceleration pedal. The car's speed (that is, body temperature) will decrease slightly but with undesirable consequences of

excessive wear on the engine, transmission, drive train, brakes, etc. Likewise, with forced reductions in body temperature there is increased stress on thermoregulation and other physiological systems. As more body heat is extracted with a normal set point, the thermoregulatory system responds by increasing heat production and reducing heat loss. This response lowers the efficacy of the method of hypothermic induction. More importantly, the forced hypothermia causes undesirable physiological effects (described above) as thermoeffectors and other physiological systems are activated to counter the reduced body temperature. In addition, the psychological stress of forced hypothermia would also be profound at this time because the subject, if conscious, would feel extremely cold and experience marked discomfort.[73] Moreover, if the subject were anaesthetised during forced hypothermia, there most probably would be an undesirable exacerbation of the duration and potency of the anaesthetic because of the reduced body temperature (see below).

On the other hand, a completely different physiological picture emerges if body temperature is reduced by a regulated rather than forced mechanism. Depending on the initial body temperature and magnitude of reduction in the set point, the onset of the regulated hypothermic response would be characterised by peripheral vasodilatation, sweating, and suppression of heat gain thermoeffectors. The subject would feel warm during the initial period of regulated hypothermia, which would alleviate the psychological stress of the hypothermic state. Activation of other physiological systems (for example, tachycardia, tachypnea, corticosteroid and epinephrine release) would be expected to be minimal during regulated hypothermia.

INTERSPECIES EXTRAPOLATION OF REGULATED HYPOTHERMIA

The majority of experimental studies that investigate the potential benefits of hypothermia have been performed in mice, gerbils, and rats. A premise in most of these studies is that the results will eventually be used to improve the understanding of the pathophysiological responses of humans. However, differences in thermoregulatory response between rodents and humans subjected to insults hampers the extrapolation process.

It must be emphasised that it is not known if larger species such as humans undergo a regulated hypothermic when subjected to an insult. Rodents have relatively large surface area:body mass ratios and are capable of rapidly lowering body temperature. As body mass increases, the surface area:body mass ratio decreases resulting in greater thermal stability. The relatively few studies suggest that the rate and overall change in body temperature after an insult is far smaller in humans as compared with rodents.[59 60] This inability to reduce body temperature in large species may be a result of their increased thermal inertia. On the other hand, the attenuation in insult induced hypothermia in large species may reflect different physiological strategies. That is, large species may have evolved alternative mechanisms to respond and recover to insults because they are unable to mount a regulated hypothermic response that is characteristic in small mammals.[60]

Acceptance and use of hypothermia as a treatment is likely to be limited by concerns of the deleterious effects of an abnormally low body temperature. Hypothermia induction during surgical anaesthesia[61] and treatment of brain injuries[57 74] is of major concern to the health of the patient. For example, an approximate 2°C decrease in core temperature increases the duration of anaesthetic recovery, causes haemodynamic instability, and depresses cognitive function.[62] Immune function also has been shown to be affected in patients allowed to become hypothermic during surgical anaesthesia.[63] Prothrombin time is significantly increased with a 3°C reduction in temperature of the blood.[75]

INTERPRETATION OF STUDIES IN HYPOTHERMIC ANIMALS

In scores of studies on the pathophysiology of insults, researchers will attempt to change the body temperature of the control group to the same level as that of the insulted animal to compare the effects of a drug or other experimental treatment. However, the body temperature of the control animal will be forced below the set point whereas the temperature of the insulted animal will be regulated below normal. Of course, these are distinct hypothermic conditions and the physiological and pharmacological responses of the animals in forced and regulated hypothermia will differ markedly. One would expect the efficacy and sensitivity to various drugs and other agents would be changed depending on whether or not body temperature is forced or regulated below normal.

Future directions: controlling the set point

Overall, many view hypothermia as a potential benefit to recovery from insult but others will probably be concerned with the possible deleterious effects of hypothermia on the subject's health. This conflict may be resolved by distinguishing and understanding the physiology of forced and regulated hypothermia. To this end, I feel that the following issues must be investigated in future research endeavours:

1 Are the mechanisms of hypothermic protection to an insult the same in small and large homeothermic species?

2 Are the CNS thermoregulatory centres of large species (for example, adult humans) wired to evoke a regulated hypothermic response when subjected to insult?

3 Forced hypothermia is commonly used to ameliorate cellular damage from insults such as ischaemia. Would regulated hypothermia be a better means of treating the insult?

4 Most importantly, is it possible to evoke a regulated hypothermia response in humans in the same manner as with smaller species? There was a tremendous amount of work in the

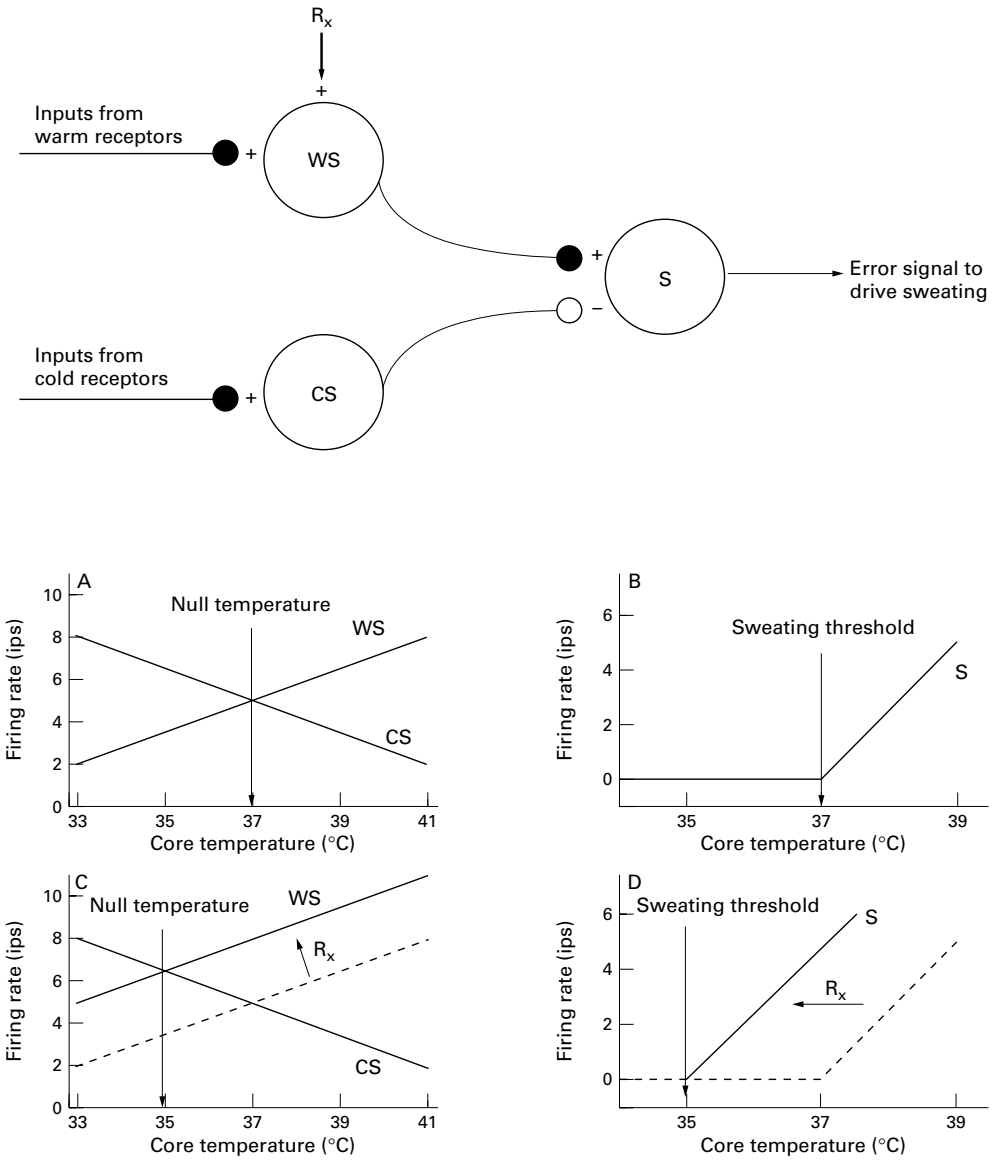

Figure 3 Conceptual neural network showing how a set point temperature can be generated and modulated to control sweating and mediate a regulated decrease in core temperature. In this scheme, a warm sensitive (WS) neuron facilitates and cold sensitive neuron (CS) inhibits the activity of an integrating neuron (S) in a 1:1 ratio. The activity from neuron S is an error signal exerting proportional control over the rate of sweating. In panel A, the intersection in activity of the WS and CS neurons results in no activity of neuron S and no sweating. Temperature below the null point results in no activity from neuron S. As temperature increases above the null point, activity of WS exceeds CS, and activity of S also increases leading to a proportional increase in sweating with rising core temperature (panel B). An agent that increases the intercept of the firing rate temperature relation of neuron WS results in a 2°C lowering of the null point where activity of WS and CS are equal (panel C). This lowers the threshold temperature for sweating by 2°C (panel D) and the system behaves as if body temperature is 2°C higher than the actual temperature. Hence, profuse sweating is elicited at a core temperature of 37°C and would theoretically continue until core temperature is reduced to 35°C. Model adapted from several sources.[9–11 64]

1960s to 1980s on the neurophysiology and neuropharmacology of the set point.[7 9 10 64 65] This wealth of data on the set point should lead to the development of agents to manipulate its control in humans and other species.

How could the set point be modified? A simple neural network illustrates how the set point temperature could theoretically be modified for relatively long periods of time (fig 3). The set point temperature is considered to be a result of the interaction in activity between warm, cold, and thermal insensitive neurons in the POAH. An agent that shifts the slope and/or intercept of the thermal sensitive neurons will result in a shift in the set point temperature. In this example of a neural network to control sweating (fig 3), an agent (R_x) has increased the intercept of the warm sensitive neurons. This causes the null temperature of equivalent activity for the warm and cold sensitive neurons to decrease by 2°C. The threshold temperature to increase sweating is thus shifted to a lower temperature. In this state, core temperature is 37°C but sweating is activated as if core temperature were 39°C. Evaporative cooling is elicited and body temperature decreases until the null temperature is reached. The same type of neural network also drives heat producing thermoeffectors. A shift in activity of the warm sensitive neurons leads to a lowering of the threshold for heat gain and heat conservation. The subject

would feel hot and suppress heat gain/conservation to allow body temperature to decrease to the new set point.

The challenge for thermal physiology is to ascertain the agent(s) that could evoke the regulated hypothermic response. Considering that a form of regulated hypothermia is rapidly evoked when ever an antipyretic agent is given to a febrile subject, it seems possible that regulated hypothermic responses could also be elicited in afebrile humans. There is a myriad of agents that could be used to lower the set point, including neurotransmitters, hormones, electrolytes, and other agents (for review, see Clark and Lipton[66] and Clark[67]). More recently, there has been a better understanding of how cytokines such as tumour necrosis factor and interleukin 10 may act as cryogens to lower the set point.[68 69] However, we know little on the efficacy of such agents to modulate the set point without causing adverse effects on the subject. It is not known how long a reduction in set point temperature could be maintained by a chemical agent without causing harm to the subject. Ideally, a therapeutic benefit of hypothermia would require that the hypothermic state be maintained for several days. The development of transmitters, hormones, or other chemicals to modulate the set point temperature independently of other physiological processes would be invaluable to basic and applied biomedical research.

Conclusion

Reducing body temperature is likely to be beneficial to humans and other species when subjected to CNS ischaemia and possibly other insults such as poisoning. The manner of achieving the reduction in body temperature, whether it is forced or regulated, may have a profound effect on the therapeutic efficacy of the hypothermia. Regulated hypothermia would seem to be the best means of achieving a therapeutic benefit of hypothermia. Our understanding of regulated hypothermia in large species such as humans is poorly understood. More research on the mechanisms of thermoregulation with special emphasis on the set point and its control is essential for future use of hypothermia as a therapeutic agent.

I thank Drs L Leon, J Fewell, L Katz, and D Sessler for their review of the manuscript. I also thank Dr A Romanovsky for his comments. This paper has been reviewed by the National Health and Environmental Effects Research Laboratory, US Environmental Protection Agency, and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

1 Busto R, Dietrich WD, Globus M, *et al*. Small differences in intraischemic brain temperature critically determine the extent of ischemic neuronal injury. *J Cereb Blood Flow Metab* 1987;**7**:729–38.
2 Chen H, Chopp M, Zhang ZG, *et al*. The effect of hypothermia on transient middle cerebral artery occlusion in the rat. *J Cereb Blood Flow Metab*1992;**12**:621–8.
3 Coulbourn F, Sutherland G, Corbett D. Postischemic hypothermia-a critical appraisal with implications for clinical treatment. *Molec Neurobiol* 1997;**14**:171–201.
4 Meden P, Overgaard K, Pedersen H, *et al*. Effect of hypothermia and delayed thrombolysis in a rat embolic stroke model. *Acta Neurol Scand* 1994;**90**:91–8.
5 Palmer AM, Marion DW, Botscheller ML, *et al*. Therapeutic hypothermia is cytoprotective without attenuating the traumatic brain injury-induced elevations in interstitial concentrations of aspartate and glutamate. *J. Neurotrauma* 1993;**10**:363–72.
6 Dietrich WD. The importance of brain temperature in cerebral injury. *J Neurotrauma* 1992;**9**:S475–85.
7 Gordon CJ. *Temperature regulation in laboratory rodents*. New York: Cambridge University Press, 1993.
8 Gordon CJ, Mohler FS, Watkinson WP, *et al*. Temperature regulation in laboratory mammals following acute toxic insult. *Toxicology* 1988;**53**:161–78.
9 Bligh J. Mammalian homeothermy: an integrative thesis. *J Thermal Biol* 1998;**23**:143–258.
10 Boulant JA, Curras MC, Dean JB. Neurophysiological aspects of thermoregulation. In: Wang LCH, ed. *Advances in comparative and environmental physiology*. Vol 4. Berlin: Springer-Verlag, 1989:117–60.
11 Gordon CJ, Heath JE. Integration and central processing in temperature regulation. *Annu Rev Physiol* 1986;**48**:595–612.
12 IUPS. Glossary of terms for thermal physiology [revised by Committee on Thermal Physiology, International Union of Physiological Sciences (IUPS)]. *Pflugers Arch* 1987;**410**: 567–87.
13 Kanosue K, Romanovsky AA, Hosno T, *et al*. "Set-point" revisited. In: Johannsen BN, Nielsen R, eds. *Thermal physiology 1997*. Copenhagen: The August Krogh Institute, 1997:39–43.
14 Kozak W. Regulated decreases in body temperature. In: Mackowiak PA, ed. *Fever: basic mechanisms and management*. 2nd ed. Philadelphia: Lippencott-Raven, 1997:467–78.
15 Kluger MJ. Fever: role of endogenous pyrogens and cryogens. *Physiol Rev* 1991;**71**: 93–127.
16 Kottke FJ, Phalen JS, Taylor CB, *et al*. Effect of hypoxia upon temperature regulation of mice, dogs, and man. *Am J Physiol* 1948;**153**:10–15.
17 Haaland K, Loberg EM, Steen PA, *et al*. Posthypoxic hypothermia in newborn piglets. *Pediatr Res* 1997;**41**:505–12.
18 Sirimanne ES, Blumberg RM, Bossano D, *et al*. The effect of prolonged modification of cerebral temperature on outcome after hypoxic-ischemic brain injury in the infant rat. *Pediatr Res* 1996;**39**:591–7.
19 Trescher WH, Ishiwa S, Johnston MV. Brief post-hypoxic-ischemic hypothermia markedly delays neonatal brain injury. *Brain Dev* 1997;**19**:326–38.
20 Wood SC. Interactions between hypoxia and hypothermia. *Annu Rev Physiol* 1991;**53**: 71–85.
21 Buchan A, Pulsinelli WA. Hypothermia but not the N-methyl-D-aspartate antagonist, MK-801, attenuates neuronal damage in gerbils subjected to transient global ischemia. *J Neurosci* 1990;**10**:311–16.
22 Miller DB, O'Callaghan JP. Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse. *J Pharmacol Exp Ther* 1994;**270**:752–60.
23 Minard FN, Grant DS. Hypothermia as a mechanism for drug-induced resistance to hypoxia. *Biochem Pharmacol* 1982;**31**:1197–203.
24 Azzimondi G, Bassein L, Nonino F, *et al*. Fever in acute stroke worsens prognosis. A prospective study. *Stroke* 1998; **29**:529–34.
25 Hindfelt B. The prognostic significance of subfebrility and fever in ischaemic cerebral infarction. *Acta Neurol Scand* 1976;**53**:72–9.
26 Reith J, Jorgensen HS, Pedersen PM, *et al*. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet* 1996;**347**:422–5.
27 Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Lancet* 1996;**347**:422–5.
28 Lee KC, Hammed DW, Kunbel S. Rodent model of renal ischemia and reperfusion injury: influence of body temperature, seasonal variation, tumor necrosis factor, endogenous and exogenous antioxidants. *Methods Find Exp Clin Pharmacol* 1993;**15**:153–9.
29 Zager RA, Altschuld R. Body temperature: an important determinant of severity of ischemic renal injury. *Am J Physiol* 1986;**251**:F87–93.
30 Gambassi G, Cerbai E, Pahor M, *et al*. Temperature modulates calcium homeostasis and ventricular arrhythmias in myocardial preparations. *Cardiovasc Res* 1994;**28**:391–9.
31 Sakuma T, Takahashi K, Ohya N, *et al*. Ischemia-reperfusion lung injury in rabbits: mechanisms of injury and protection. *Am J Physiol* 1999;**276**:L137–45.
32 Doull J. The effect of physical environmental factors on drug response. *Essays Toxicol* 1972;**3**:37–63.
33 Fuhrman FA. The effect of body temperature on drug action. *Physiol Rev* 1946; **26**:247–4.
34 Yamamoto H, Fujii K, Hayakawa T. Inhibitory effect of cold stress on lung tumours induced by 7,12-dimethylbenz[a]anthracene in mice. *J Cancer Res Clin Oncol* 1995; **121**:393–6.
35 Yamaguchi S, Shimojo N, Sano K, *et al*. Effects of environmental temperatures on the toxicity of methylmercury in rats. *Bull Environ Contam Toxicol* 1984;**32**:543–9.
36 Dyer RS, Howell WE. Triethyltin: ambient temperature alters visual system toxicity. *Neurobehav Toxicol Teratol* 1982;**4**:267–71.
37 Harri MN. Effect of body temperature on cardiotoxicity of isoprenaline in rats. *Acta Pharmacol Toxicol* 1976;**39**:214–24.
38 Watkinson WP, Gordon CJ. Caveats regarding the use of the laboratory rat as a model for acute toxicological studies: modulation of the toxic response via physiological and behavioral mechanisms. *Toxicology* 1993;**81**:15–31.
39 Li GC, Hahn GM, Shiu EC. Cytotoxicity of commonly used solvents at elevated temperatures. *J Cell Physiol* 1977; **93**:331–4.

40 Herman TS, Teiche B, Cathcart KN, *et al*. Effect of hyperthermia on cis-diamminedichloroplatinum(II) (rhodamine)2[tetrachloroplatinum(II)] in a human squamous cell carcinoma line and a cis-diamminedichloroplatinum(II)-resistant subline. *Cancer Res* 1988;**48**:5101–5.
41 Prosser CL. Temperature. In: Prosser CL, ed. *Comparative animal physiology.* Philadelphia: WB Saunders, 1973:362–428.
42 Lei B, Tan X, Cai H, *et al*. Effect of moderate hypothermia on lipid peroxidation in canine brain tissue after cardiac arrest and resuscitation. *Stroke* 1994;**25**:147–52.
43 Astrup J. Energy-requiring cell functions in the ischemic brain. Their critical supply and possible inhibition in protective therapy. *J Neurosurg* 1982;**56**:482–97.
44 Finn DA, Bejanian M, Jones BL, *et al*. Temperature affects ethanol lethality in C57BL/6, 129, LS and SS mice. *Pharmacol Biochem Behav* 1989;**34**:375–80.
45 Bejanian M, Finn DA, Syapin PJ, *et al*. Body temperature and ethanol pharmacokinetics in temperature-challenged mice. *Alcohol* 1990;**7**:331–7.
46 Gordon CJ, Yang Y. Thermoregulatory response to chemical toxicants and other insults: extrapolation from experimental animal to human. *N Y Acad Sci* 1997; **813**:835–48.
47 Gordon CJ. Behavioral thermoregulatory response to chlorpyrifos in the rat. *Toxicology* 1997;**124**:165–71.
48 Gordon CJ, Stead AG. Effect of alcohol on behavioral and autonomic thermoregulation in mice. *Alcohol* 1986;**3**:339–43.
49 Clark DJ, Fewell JE. Decreased body-core temperature during acute hypoxemia in guinea pigs during postnatal maturation: a regulated thermoregulatory response. *Can J Physiol Pharmacol* 1996;**74**:331–6.
50 Gordon CJ, Fogelson L. Comparative effects of hypoxia on behavioral thermoregulation in rats, hamsters, and mice. *Am J Physiol* 1991;**260**:R120–5.
51 Gordon CJ. The role of behavioral thermoregulation as a thermoeffector during prolonged hypoxia in the rat. *J Thermal Biol* 1997;**22**:315–24.
52 Romanovosky A,. Shido O, Sakurada S, *et al*. Endotoxin shock: thermoregulatory mechanisms. *Am J Physiol* 1996; **270**:R693–703.
53 Gordon CJ. Induction of regulated hypothermia in mice by urine administration. *J Thermal Biol* 1990;**15**:97–101.
54 Gordon CJ. 24-hour control of body temperature in the rat: II. Diisopropyl fluorophosphate-induced hypothermia and hyperthermia. *Pharmacol Biochem Behav* 1994;**49**:747–54.
55 Leikin JB, Aks S, Andrews S, *et al*. Environmental injuries. *Dis Mon* 1997;**43**:809–916.
56 Plattner O, Kurz A, Sessler DI, *et al*. Efficacy of intraoperative cooling methods. *Anesthesiology* 1997;**87**:1089–95.
57 Clifton GL, Allen S, Berry J, *et al*. Systemic hypothermia in treatment of brain injury. *J. Neurotrauma* 1992;**9**:S487–95.
58 Giesbrecht GG, Goheen MS, Johnston CE, *et al*. Inhibition of shivering increases core temperature afterdrop and attenuates rewarming in hypothermic humans. *J Appl Physiol* 1997;**83**:1630–4.
59 Gordon CJ. Toxic-induced hypothermia and hypometabolism: do they increase uncertainty in the extrapolation of chemical toxicity from experimental animal to humans? *Neurosci Biobehav Rev* 1991;**15**:95–8.
60 Gordon CJ. Homeothermy: Does it impede the response to cellular injury? *J Thermal Biol* 1996;**21**:29–36.
61 Sessler DI. Perioperative thermoregulation and heat balance. *Ann NY Acad Sci* 1997;**813**:757–77.
62 Lenhardt R, Marker E, Goll V, *et al*. Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997;**87**:1318–23.
63 Beilin B, Shavit Y, Razumovsky J, *et al*. Effects of mild perioperative hypothermia on cellular immune responses. *Anesthesiology* 1998;**89**:1133–40.
64 Hammel HT. The set-point in temperature regulation: analogy or reality. In: Blight J, Moore RE, eds. *Essays on temperature regulation.* Amsterdam: North-Hollan, 1972: 121–37.
65 Hensel H. Neural processes in thermoregulation. *Physiol Rev* 973;**53**:948–1016.
66 Clark WG, Lipton JM. Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents: II. *Neurosci Biobehav Rev* 1985; **9**:299–371.
67 Clark WG. Changes in body temperature after administration of antipyretics, LSD, Δ^9-THC and related agents: II. *Neurosci Biobehav Rev* 1987;11:35–96.
68 Leon LR, White AA, Kluger MJ. Role of Il-6 and TNF in thermoregulation and survival during sepsis in mice. *Am J Physiol* 1998;**275**:R269–77.
69 Leon LR, Kozak W, Rudolph K, *et al*. An antipyretic role for interleukin-10 in LPS fever in mice. *Am J Physiol* 1999;**276**:R81–9.
70 Stolwijk JAJ, Hardy JD. Regulation and control in physiology. In: Mountcastle VB, ed. *Medical physiology*. Vol 2. St. Louis: CV Mosby, 1974:1343–58.
71 Romanovosky A, Shido O, Sakurada S, *et al*. Endotoxin shock: thermoregulatory mechanisms. *Am J Physiol* 1996; **270**:R693–703.
72 Henderson RA, Whitehurst ME, Morgan KR, *et al*. Reduced oxygen consumption precedes the drop in body core temperature caused by hemorrhage in rats. *Shock* 2000;**13**:320–4.
73 Kurz A, Sessler DI, Narzt E, *et al*. Postoperative hemodynamic and thermoregulatory consequences of intraoperative core hypothermia. *J Clin Anesth* 1995;**7**:359–66.
74 Marion DW, Leonov MD, Ginsberg M, *et al*. Resuscitative hypothermia. *Crit Care Med* 1996;**24** (suppl):S81–9.
75 Rohrer MJ, Tatale AM. Effect of hypothermia on the coagulation cascade. *Crit Care Med* 1992;**20**:1402–5.