Current topic**Fever—the fire of life**

D HULL

University Hospital, Queen's Medical Centre, Nottingham

The 'fire of life' is the title of Kleiber's book on animal energetics. He wrote of the relation between body size and metabolic rate.¹ The elephant is more economic than the mouse in that it supports its living mass with less energy per unit body weight and thus appears at an advantage. However it is the exposed surface area that determines the environment at which the body works most efficiently, and expressed as energy per unit surface area the mouse has the edge over the elephant. These are mysterious matters of considerable importance to those who produce meat for human consumption. They are of relevance to paediatricians in that newborn infants emerge from one set of circumstances into very different ones, and have to reach a different balance to that of the parents who look after them. If we are to help them when they are sick we have to know of these adjustments, and that was what I proposed to speak of when I chose my title for the Still lecture, 'The fire of life'. But I changed my mind and instead spoke about fever, for it has again become of interest. In this context the 'fire of life' is not the metabolic cost of living but the fever that may cleanse or damage the body. It still allowed me to do what I wish, which is to illustrate an aspect of developmental biology relevant to a current clinical problem.

Is a fever therapeutic or harmful?

This is an old question. The arguments in support are at three levels. Firstly, the high principle; surely such a powerful and consistent reaction, which is seen in poikilothermic as well as homoeothermic animals, must have some survival value or it would not have persisted. Secondly, animal investigations; for example the studies of Kruger and colleagues on the reptile *Dipsosaurus dorsalis* who found that when bacteria were injected the survival was much greater in those which were allowed to select a warmer environment.² Thirdly, clinical observations; Rufus of Ephesus (2nd century) observed '...

if there were a physician skilled enough to produce a fever, it would be useless to seek any other remedy against disease'; Sydenham (17th century) wrote that 'Fever is a mighty engine which Nature brings into the world to the conquest of her enemies'; Du Bois in his book on fever ended, 'Finally one is faced with the question as to whether or not fever in disease is beneficial. The literature on this subject is extensive and inconclusive' and concluded that 'fever therapy has proved relatively safe and beneficial in many diseases' but that was before the time of antibiotics and steroids.³

The alternative arguments run; first on high principle: how can a reaction that places such demands upon the body's reserves enhance its chance of survival? Secondly, animal investigations; it has not been possible to satisfactorily replicate the reptile studies in mammals, and it does not appear to be demonstrable in all lizards either. Clinical observations would suggest that the wide spread use of antipyretics has not been to the subject's disadvantage, but that, in the main, has been after the use of antibiotics.

If high body temperatures assist in the rejection of microscopic invaders then the wide variation in the deep body temperatures found in different mammals and birds takes on a greater interest, does the body temperature determine in part the organisms which colonise or infect us? The table shows typical temperatures.

Clinical issues**(1) SIGNAL OF DISEASE**

Parents recognise when their child has a fever, they know that to be a sign that their infant is not well, and usually seek medical advice. There are a number of statements in the medical literature from the United States advising parents at what level of temperature they should call their doctor. As part of our aim of increasing parent involvement in the care of their sick child in hospital we have explored the

Table Average rectal temperature of mammals and birds (for Brody, 1964*)

Animal	Temperature (°C)
<i>Mammals</i>	
Elephant	36.0
Man	37.0
Rat	37.3
Horse	38.0
Cattle	38.5
Sheep/pig	39.0
Rabbit	39.5
Goat	40.0
<i>Birds</i>	
Turkey, goose, duck, owl, pelican, vulture	40–41
Fowl, pigeon, quail, sparrow, starling	42–43

feasibility of parents recording the temperature; this if nothing else causes one to reconsider just what information can be gained from the temperature, pulse, and respiration charts.

(2) INFECTION IN THE NEWBORN

The newborn infant is subject to infections but rarely reacts with a fever. Theoretically if fever is beneficial then newborn infants like older children might benefit when they have an infection if they were nursed at a slightly higher temperature. It raises the questions as to when and why infants begin to respond to an exogenous pyrogen with a fever.

(3) SUDDEN INFANT DEATH

There is growing evidence that hyperpyrexia might be the final mechanism in at least some infants who die unexpectedly at home.^{5 6} This might be because they are overwrapped and the capacity to lose heat is overpowered. Alternatively it maybe that at the critical age period they develop a response to pyrogen for the first time and generate a fever, which might not be well controlled or may present the infant with a challenge to which they cannot adequately respond because of their thermal environment. The striking statistic of postneonatal infant death in the United Kingdom is that death occurs at a certain age, suggesting a development related factor, and more often in the winter than the summer, which suggests a precipitating infection.

(4) COOL WASHES AND FEBRILE FITS

Why some older infants have a fit when they have a fever is another mystery. The current recommendation to parents of a child who has had a febrile fit is to keep their infant cool with sponging, and to suppress the fever with an antipyretic. Both have

been shown to lower the temperature in febrile infants, whether they reduce the incidence of fits is less clear. They are both difficult to administer in time. Cool sponging will increase the infants' metabolic rate while antipyretics may reduce it. There ought to be some way of deciding which one is the better approach.

In light of these and other issues now seemed to be an appropriate time to review what is currently known about the development of the response to pyrogen after birth and the development of the thermoregulatory mechanisms, and then to shape our current understanding as a guide to clinical practice and future research.

The response to endotoxin

There are many substances which if injected provoke a fever (exogenous pyrogens⁷). The lipopolysaccharides wrapping bacteria are among the more powerful and are widely used in animal studies. The injection of these endotoxins activates the ubiquitous travelling monocytes or like acting cells, which respond by producing interleukin 1. This chemical (or family of similar chemicals) acts at a number of sites.^{8 9} Its action on the brain is to increase the body temperature, encourage sleep, suppress the appetite, and release neuropeptides. Its action on the liver results in the production of the acute phase proteins, the suppression of albumin production, and the inhibition of lipoprotein lipase activity and thus fat utilisation. It enhances the local inflammatory response, and encourages the healing processes by increasing capillary leak, releasing vasodilators, while inducing endothelial cell proliferation and initiating clot formation. But its major effect is perhaps on the haematopoietic and lymphoid cells. It stimulates new cell formation and acts on T cells and provokes the release of interleukin 2, a lymphokine, which activates T and B cell formation. All in all it is a very busy protein.

The weight of its various effects in any one situation may well vary, however taken at its simplest it would seem that the pyrogen effect is linked to all these other activities and a fever properly recorded must be a measure of some of them. The endogenous pyrogen of the older literature is thought to be interleukin 1b.

The production of a fever

Three steps are involved in the development of a fever; first, the invading organism reacts with the phagocytosing monocyte, which in turn releases endogenous pyrogen; second, the endogenous

Fig 1 Three steps in the induction of a fever. BAT=brown adipose tissue.

pyrogen (interleukin 1b) acts on the central nervous control systems of thermoregulation in the hypothalamus; and third, the thermoregulatory system responds by raising the body temperature, this it may do by a behavioural response—for example, moving to a warmer place, or by an increase in thermoregulatory heat production (fig 1). There is

some evidence to suggest that the bacterial material (exogenous pyrogen) might itself act on the central mechanisms and cause a fever, and if the illness causes hypermetabolism then that itself could result in a fever. In most circumstances it seems likely that the three steps are required. Thus if no fever occurs, as may be the case in the newborn, then it might be due to differences in responsiveness at any of the stages in the sequence.

The development of a febrile response can be demonstrated by injecting endotoxin. Fig 2 shows the mean rise in body temperature and rate of oxygen consumption of rabbits aged 3 to 5 days after intraperitoneal injection of lipopolysaccharide from the shell of *Escherichia coli* bacteria. The rise was followed by a rise in colonic temperature. The rabbits were initially placed in an ambient temperature within their thermoneutral range and this temperature was not changed for the duration of the study. This response is similar to that found in adult rabbits and has two phases, a rise after a latent period of 15 to 20 minutes reaching a peak in 40 to 50 minutes followed by a fall only to begin to rise again in the 60 to 70 minute period. However, similar rabbits on the day of birth showed no such response. These results are similar to those reported earlier by Székely and Szélenyi.¹⁰ Clearly something is developing rapidly after birth, presumably induced by the birth process or the new environment.

Similar findings have been observed in other species—for example, guinea pigs^{10 11} and lambs.¹² Thus it would seem that there is some hesitancy after birth in the response to pyrogen but in the guinea pig and lamb as well as rabbits an unequivocal response can be demonstrated on the second or third day of life. It does seem on the evidence that is available that in general the presence or not of the response varies with the dose and that young animals need a relatively larger dose than older

Fig 2 The mean rates of oxygen consumption and colonic temperatures in rabbits on the day of birth and aged 3-5 days, n=10 (from J Vinter and D Hull, unpublished).

animals, but the magnitude of the response, once elicited, does not vary with age and increasing the dose does not increase the magnitude of response.

Behavioural thermoregulatory responses to pyrogen

Endogenous pyrogen acts by adjusting the thermoregulatory response such that a higher body temperature is defended. This may be either by behavioural or automatic responses. The former are preferred because they put less demand on energy reserves. Newborn rabbits show behavioural thermoregulatory responses from the moment of birth, ambient temperature appears to be the most powerful stimulus to their activity, it draws them towards their mother and it draws them towards each other in a cool environment. In a warm environment they separate.¹³ Fig 3 shows the behavioural responses of 3 to 5 day old rabbits injected with endotoxin. The rabbits given endotoxin selected a higher environmental temperature.

Fig 3 Selected environmental temperatures and colonic temperatures in rabbits aged 3–5 days in littermates not injected and injected with endotoxin, $n=10$ (From J Vinter and D Hull, unpublished).

It is reasonable to ask that if newborn rabbits are stimulated by pyrogen what behavioural response might they make? It is interesting that the young move themselves around within a litter so as to maintain body temperatures, presumably the febrile one might act to stay in the midst of the group longer.

The rabbits injected with endotoxin chose an environment that gave them a higher deep body temperature than that achieved by the rabbits kept within their original thermoneutral range. The reasons became clear after more detailed study of the automatic or physiological thermoregulatory response.

Automatic or physiological thermoregulatory response to pyrogen

The physiological thermoregulatory adjustments to different environmental temperatures are shown in the format used by Mount (fig 4).¹⁴ The values are for a term infant, nursed naked, and assumes that the responses, sweating, vasomotor and postural changes, and thermogenesis proceed in sequence and do not overlap, and that the deep body temperature is held at 37° (which in the event it does not), and that the infants physical characteristics relevant to heat exchanges stay constant.

It is generally suggested that pyrogen resets the thermoregulatory set point upwards. Thus it might be anticipated that if the individual is exposed to pyrogen, but is held in the same environment, then thermogenesis would increase and that increase would be formed of two components (fig 5). The first would be thermoregulatory thermogenesis and the second an increase in the minimal rate due to the so called Q_{10} effect. The van't Hoff/Arrhenius relationship states that the rate of a chemical reaction is proportional to the temperature, biochemical reactions have a Q_{10} between 2 and 3, thus for every degree rise the metabolic rate might be expected to increase 10%. Studies on man and adult animals have shown a rise in metabolic rate with a fever. It is not always clear whether thermoregulatory thermogenesis has been excluded and it appears to be a very variable phenomenon. Thus while the metabolic rate of poikilothermic animals may increase with surrounding and body temperatures the evidence that homeothermic mammals 'obey' the Q_{10} effect remains uncertain.

Making the necessary investigations to establish whether the situation illustrated in fig 5 is the true one is difficult because of the many interfering variables, activity, feeding, restraint, sleep, etc. In this respect the newborn rabbit, which feeds once a day and does little else, is particularly suitable. Fig 6

Fig 4 Theoretical average values of heat exchange and deep body temperature of naked term infants based on best available information and making certain assumptions (see text and Wheldon 1982¹⁵).

Fig 5 The theoretical effect of changing the thermoregulatory 'set point' in the normal and febrile infant.

illustrates the findings on two groups of rabbits aged 3 to 5 days, one of which was given pyrogen before the observations.

The results are of interest for three reasons. Firstly, there was no Q_{10} effect. In other words when the rabbits were in a thermoneutral environment for their new set temperature they did not have an increase in metabolic rate. There is no inevitable cost for a fever. The reason why the rabbits given pyrogen and kept in their original thermoneutral range (fig 1) had an increased metabolic rate is because they then perceived that environmental temperature as cool.

Secondly, the association between metabolic rate with thermal environment did not alter: although the set point was adjusted upwards as shown in fig 5, the gradient changed. The gradient is a measure of thermal insulation which is most easily calculated if the colonic temperature remains constant. But in rabbits, as in newborn infants, the colonic temperature does not stay constant but slides down with the

ambient temperature. The reason for this is not clear, but its effect is to allow some thermal control over a wider range of thermal conditions. After administration of endotoxin the gradient in the fall of rectal temperature was greater. The effect of this was that at thermoneutral temperatures the endotoxin resulted in much higher colonic temperatures but the difference with those not given endotoxin decreased as the ambient temperature fell so that endotoxin made no difference to body temperatures at ambient temperatures at the lower end of the range of thermal control.

Thirdly, the change in gradient indicates that the pyrogen acts to influence the gain rather than shift the set point. Two models have been proposed for the central control of temperature and to explain the effects of pyrogen.¹⁶ The first assumes a central mechanism that has some inherent prescribed set temperature that the system defends. The second proposes that pyrogens act by influencing the responsiveness to feed back information and thus affect the body temperatures. If pyrogen acted to change the set point it would produce the theoretical response illustrated in fig 5, if it altered the gain it would in effect produce the response seen in 3 to 5 day old rabbits illustrated in fig 6. Thus if the fever has any beneficial effect then it will be most effective in a warm environment when it will make least demand in the new thermoneutral environment.

The practical implication of this is that if the aim of management is to remove the burden of the metabolic response to fever then the appropriate step would be to keep the infant warm. A problem arises with a fluctuating temperature.

Development of thermoregulatory control

The development of fever depends on thermoregulatory control and effective thermoregulatory mechanisms either behavioural or thermoregulatory thermogenesis. In some mammals they are present on the day of birth. But this is not so in all mammals. For example, the hamster on the day of birth is poikilothermic in that it is unable to show any response to changes in environmental temperature and has no control over its own body temperature. The mother controls the temperature of her young by the time she spends in the nest: she is the source of heat as well as insulation. By eight days the young hamster shows thermotaxis, that is it moves to a warm temperature but not in a controlled way, by 12 days it shows effective behavioural thermoregulation, and by 16 days it has developed effective automatic thermoregulatory mechanisms. The development of thermogenesis in the hamster would appear to illustrate the concept popularised by Barcroft and

Fig 6 Mean values of the heat exchange and colonic temperatures of rabbits, 3–5 days old, in control (open symbols) and after injection of endotoxin (closed symbols) (J Vinter and D Hull, unpublished).

beloved by developmental physiologists, that 'ontogeny follows phylogeny'. What seems clear is that the central mechanisms of thermoregulatory control develop in advance of the thermogenic effector responses. In most newborn mammals that means thermogenesis in brown adipose tissue. In some larger mammals and in the guinea pig, rabbit, and kitten thermoregulatory control (behavioural and automatic) is demonstrable on the first day of life. In them the absence of a response to endotoxin over the first days cannot be explained on the basis that the body could not effect the increase in temperature provided the investigation was done in an appropriately warm environment. The delay would seem to reside in the production of pyrogen or its activity centrally.

The human term newborn infant shows thermoregulatory thermogenesis on the day of birth, though it may increase in magnitude over the first hours of life. It can also make behavioural responses if allowed. The clinical impression that newborn infants do not react with a fever requires re-examination when due consideration is given to the environmental temperature. Precise observations would suggest that a febrile response does develop soon after birth. Observations on newborn lambs

suggest that previous exposure to endotoxin may accelerate the development of the response.¹²

Immature infants are a different matter, or are they? Certainly they do not develop pyrexias, but is that because they only have a limited thermogenic capacity (none has been found in infants under 28 weeks' gestation though they have brown adipocytes, but some response is seen in infants 32 weeks and over¹⁷) or is it because they are nursed in such a way that any fever they develop would immediately be corrected by adjustment in their environment such that they strive to increase their temperature but are unable to succeed. Such activity might well present them with an unnecessary metabolic burden.

The human infant remains dependent on the awareness of his or her parents for behavioural reactions for some months after birth, the infant left alone depends on automatic responses. Those at birth are primarily thermoregulatory thermogenesis in the cold and sweating when it is too warm. Although all the sweat glands are present at birth, and sweating on the forehead appears profuse, the infant's capacity to lose extra heat by this mechanism is comparatively limited. Thus as the infant grows at least two changes are occurring: the sweat glands may be becoming more efficient and the infant may be shifting from non-shivering to shivering thermogenesis. The timing of these events is not known.

Conclusions

In answer to the clinical questions posed it would seem that measuring an infant's body temperatures and interpreting them in the light of the environmental conditions may be even more instructive than we thought, we need to discover to what extent it reflects the other activities of interleukin.

In the newborn we might be able to do much more to meet the sick infant's needs by adjusting some of our responses. For example, it would be interesting to know if immature infants with an infection have relatively high metabolic rates and would benefit by being nursed in a warmer environment, and we need to explore the quality of the other aspects of the bodies response to interleukin.

As for hyperthermia in older infants, there may be a time when the thermoregulatory system undergoes critical stages in development and the generation of interleukin may also be a variable and measurable response which might be inducible and

possibly open to beneficial influence. Infants are particularly vulnerable to overheating if they experience fluctuating exposure to pyrogens while being nursed in the same thermal conditions.

There can be no doubt that cool washes if they lower the body temperatures will in so doing increase the metabolic rate. Thus if a fever is hazardous and needs to be corrected cool washes, while of value in an emergency, are a poor alternative to an antipyretic.

What Du Bois said forty years ago is still true, 'There is still much to be learned about fever'.³

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References

- Kleiber M. *The fire of life and introduction to animal energetics*. New York: John Wiley, 1961.
- Kruger MJ. Is fever beneficial? *Yale J Biol Med* 1986;**59**:89–95.
- Du Bois EF. *Fever and the regulation of body temperature*. Springfield: CC Thomas, 1948.
- Brody S. *Bioenergetics and growth*. New York: Hafner Publishing Company, 1964.
- Bacon CJ. Overheating in infancy. *Arch Dis Child* 1983;**58**: 673–4.
- Stanton AN. Overheating and cot death. *Lancet* 1984;**ii**: 1199–201.
- Dinareello CA, Wolff SM. Exogenous pyrogens. In: *Pyretics and antipyretics*. Milton AS, ed. Berlin: Springer-Verlag, 1982:—.
- Dinareello CA. Interleukin 1. *Rev Infect Dis* 1984;**6**:51–95.
- Strober W, James SP. The interleukins. *Pediatr Res* 1988;**24**: 549–57.
- Székely M, Szélenyi Z. The pathophysiology of fever in the neonate. In: *AS Milton, ed. Pyretics and antipyretics*. Berlin: Springer-Verlag, 1982:—.
- Blatteis CM. Postnatal development of pyrogenic sensitivity in guinea pigs. *J Appl Physiol* 1975;**39**:251–7.
- Kasting NW, Veale WL, Cooper KE. Development of fever in newborn lambs. *Am J Physiol* 1979;**236**:184–7.
- Hull J, Hull D. Behavioural thermoregulation in newborn rabbits. *Journal of Comparative and Physiological Psychology* 1982;**96**:143–7.
- Mount LE. *Adaptation to thermal environment*. London: Edward Arnold, 1979.
- Wheldon AE. Heat exchange between the newborn baby and the environment. Nottingham: Nottingham University, 1982. (PhD thesis.)
- Mitchell D, Snellen JW, Atkins AR. Thermoregulation during fever, change of set point or change of gain. *Pflugers Arch* 1970; **321**:293–302.
- Wheldon AE, Hull D. Incubation of very immature infants. *Arch Dis Child* 1983;**58**:504–8.

Correspondence to Professor D Hull, Department of Child Health, Floor E, East Block, University Hospital, Queen's Medical Centre, Nottingham NG7 2UH.