Fever in Namib and Other Ectotherms

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We examine the role of fever in the context of the evolutionary implications of host-pathogen interactions. Some ectotherms elevate their body temperatures behaviourally, following administration of pathogenic bacteria or other potential pyrogens. In a few species, the elevated temperature has been demonstrated to have positive survival value for the host. Representatives of all classes of vertebrate ectotherm have been reported to develop fever, as have representatives of the Arthropoda and Annelida, but not the Mollusca. We do not think that fever is ubiquitous amongst vertebrate ectotherms, however; we have not been able to obtain fever in seven African reptile species we have tested.

Studies of reactions of Namib ectotherms to potential pyrogens are important for several reasons. One is that some Namib species have selected body temperatures in the mammalian range, higher than most ectothermic species. Another is that the Namib Desert provides a suitable environment for studying endemic ectotherms in their natural habitat. The tenebrionid beetle *Onymacris plana* selected warmer than normal substrate temperatures, in a thermal gradient chamber, following administration of large doses of the endotoxin of gram-negative bacteria. However, the endemic lizard species *Aporosaura anchietae* and *Angolosaurus skoogi* showed no thermoregulatory responses to potential pyrogens. Future studies on the survival value of fever should include analysis of non-thermal as well as the traditional thermal components, which may have evolved separately. Also, studies are required of naturally-infected animals in their natural habitats.

FEVER AND EVOLUTION

Fever is a complex biological response of a host animal subjected to pathological insults, including infection, inflammation, tissue necrosis, antibody-antigen reactions and malignancy (Hellon, Townsend, Laburn and Mitchell, 1990). In addition to the characteristic rise in body temperature, the febrile response, at least in mammals, has several characteristic biochemical features: release of acute-phase proteins (e.g., C-reactive protein and fibrinogen), activation of lymphocytes and macrophages, and changes in serum metallic ion concentrations (decrease of iron and zinc, increase of copper) (Dinarello, Cannon and Wolff, 1988). Fever is also associated with gross behavioural changes, for example somnolence in several mammals, and both somnolence and malaise in humans (Feldberg, 1975).

Fever is a metabolically costly phenomenon; for each degree Celsius rise in body temperature, energy requirements increase by 10 % or more (Kluger, 1986). Fever also suppresses appetite, so compensatory increases in food intake usually do not occur, and febrile animals enter negative nitrogen balance and tend to lose mass.

The biochemical and physiological features of the host response that occurs during fever are largely independent of the cause of the fever. For example, the same pattern of events occurs whether the host is responding to gram-negative infection, viral infection, protozoal infection, crush injury or incompatible blood transfusion. The similarity of features arises primarily because most, if not all, of the host defence reactions have a common biochemical mediator, namely endogenous pyrogen (EP). EP is a hormone-like polypeptide, or family of polypeptides, released by macrophages, and other cells of the host, in response to any one of a variety of pathological stimuli. Four EPs have been identified, namely interleukin 1 (IL 1) and interleukin 6 (IL 6), tumour necrosis factor and interferon (Hellon *et al.*, 1990); they have little or no amino acid homology, but remarkably similar biochemical action (Dinarello *et al.*, 1988).

From the neo-Darwinian point of view, it would be anomalous for a biological phenomenon to exist, which is metabolically costly and which has similar biochemical and physiological features irrespective of the stimulus and host species, unless the phenomenon has survival value for the host. Indeed, such philosophical arguments in favour of a survival value for fever have been expressed for at least 2000 years (Kluger, 1981). However, it has proved surprisingly difficult either to show quantitatively that fever indeed favours the host's survival, or to identify components of the febrile response beneficial to the host (Ewald, 1980). Only recently has it become clear that the release of EP contributes to the host's survival in infection, and in other conditions like malignancy (Dinarello, Conti and Mier, 1986; Duff, 1986). What is still not established satisfactorily is whether pyrexia, the high body temperature characteristic of fever, *per se* has any survival value for the host (Banet, 1983; Kluger, 1986; Blatteis, 1986; Banet, 1986; Hellon *et al.*, 1990).

Pyrexia in endotherms is very different from other forms of hyperthermia (Stitt, 1979; Mitchell and Laburn, 1985). In

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pyrexia, the thermoregulatory system is neither malfunctioning nor overwhelmed. On the contrary, a well coordinated set of thermoregulatory effectors, the nature of which depends on ambient temperature, is brought into play to elevate the temperature to the febrile level, at which it is actively regulated. The thermoregulatory system behaves as if its set-point has been reset at an elevated level. Consequently, attempts to restore 'normal' temperature by physical cooling of the host are counteracted by additional heat generation and conservation (Mitchell and Laburn, 1985).

As one might expect intuitively, many of the biochemical components of the febrile response appear to be more effective in host defence at elevated host temperature (Roberts, 1979; Kluger, 1986). For example, the combination of high temperature and low serum iron concentration which occurs in fever is inimical to some species of bacteria (Kluger and Rothenburg, 1979). Elevation of body temperature to typically febrile levels, along with other forms of stress, induces production of heat shock proteins, which protect cells against subsequent stress (Barbe, Tytell, Gower and Welch, 1988). In *Drosophila,* haematocytes are immune-competent at 29 °C but not 21 °C (Nappi and Carton, 1985). Nevertheless, there is no consistent relationship between body temperature and host mortality in febrile disease. Indeed, some reports suggest that the high body temperature actually compromises the host. Some of these reports are based on epidemiological studies; for example, a group of untreated patients with pneumococcal pneumonia showed increased mortality with increasing body temperature (Bennett and Nicastri, 1960). Others derive from experimental elevation of the body temperature to febrile levels, by cooling the hypothalamus and thereby initiating heat conservation; this procedure reduced survival in rats following *Salmonella* infection (Banet, 1979).

Both epidemiological and experimental investigations of the possible survival value of pyrexia in humans and other endotherms tend to be confounded by the relatively narrow range of body temperatures within which endotherms thermoregulate, even when febrile. Pyrexial mammals and birds seldom reach body temperatures more than 2,5 °C above normal deep body temperature (Hellon *et al.,* 1990). This obstacle was overcome when Vaughn, Bernheim and Kluger (1974) (through an act of lateral thinking) successfully induced fever in an ectotherm[1], the desert iguana *Dipsosaurus dorsalis.*

Vaughn and her colleagues injected killed *Aeromonas hydrophila* (now called *Aeromonas sobria*, according to Muchlinsky, Stoutenburgh and Hogan, 1989), a gram-negative bacterium pathogenic in lizards, as well as in other animals, into desert iguanas kept in a photothermal gradient chamber. Following *A. hydrophila* injection, the lizards selected warmer parts of the chamber than they did following injection of the same volume of saline. Their body temperatures consequently rose. The peak elevation, about 2 °C, was very similar to that usually exhibited by febrile endotherms.

With hindsight, it does not seem anomalous that an animal could become pyrexial through primarily, or solely, behavioural mechanisms; behavioural mechanisms supplement autonomic mechanisms in fever in endotherms (Cabanac, 1972).

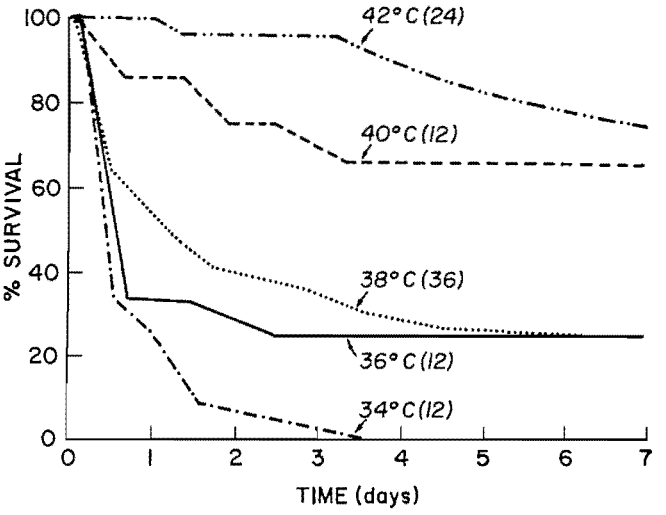

Fig. 1.

Survival of five groups of desert iguana *Dipsosaurus dorsalis,* maintained at temperatures between 34 °C and 42 °C following intracardiac injection of the live bacterium *Aeromonas hydrophila.* Numbers in parentheses are initial numbers of lizards in each group. From Kluger, Ringler and Anver (1975), by copyright permission of the American Association for the Advancement of Science.

For example, selection of warmer clothing is a common thermoregulatory behaviour in humans developing fever, initiated by the conscious sensation of feeling cold. Moreover, the biochemical mechanisms involved in the neural control of behavioural thermoregulation in ectotherms seem to be similar to those involved in endothermic thermoregulation (Bligh, Louw and Young, 1976). Before Vaughn's experiments, however, endothermy implicitly was considered a prerequisite for pyrexia.

The paper by Vaughn and her colleagues (1974) actually was not the first to report elevation in the body temperature of an ectotherm following infection. More than a decade earlier, Sauerlander and Kohler (1961) had published a brief paper describing experiments in which the cockroach *Periplaneta americana* was inoculated with bacteria; body temperature was elevated by up to 12,6 °C, and remained elevated for days. However, the cockroaches were kept in a constant temperature environment (20 °C) throughout, so the response reported would require the insects to have manifested a degree of endothermy they are not known to possess. No subsequent studies have confirmed the phenomenon, and the paper tends to be disregarded by fever experts.

If ectotherms are maintained in an isothermal environment, they necessarily adopt the temperature of the environment, except for very brief periods of hyperthermia due to muscle contraction, a fact exploited to assess the advantages of pyrexia in lizards (Kluger, Ringler and Anver, 1975). Five groups of *D. dorsalis* were infected with live *A. hydrophila,* and each group was maintained for a week at a fixed temperature between 34 °C and 42 °C. The consequences for survival are

[1]The term 'ectotherm' describes an animal that relies mainly on environmental sources of thermal energy for thermoregulation; such animals usually have a high coefficient of variation of body temperature, that is, they are also poikilothermic.

shown in Fig. 1; the higher the ambient temperature (and therefore the body temperature), the greater the proportion of animals which survived the infection. In separate experiments, infected lizards were provided with a thermal mosaic in a photothermal gradient chamber, and were given the antipyretic drug salicylate. They no longer sought out warmer environments and their survival was reduced (Bernheim and Kluger, 1976*b*).

Reduced survival in ectotherms prevented from attaining behavioural pyrexia apparently is not confined to lizards. Covert and Reynolds (1977) subsequently showed that mortality in the goldfish *Carassius auratus,* infected with live *A. hydrophila,* also increased as body temperature was reduced from 32,7 °C to 25,5 °C. More recently, Boorstein and Ewald (1987) have shown that inoculation of the grasshopper *Melanoplus sanguinipes* with the pathogenic protozoan *Nosema acridophagus* resulted in the grasshoppers selecting a body temperature of about 40 °C, rather than their normal 34 °C. In a subsequent experiment, maintaining a group of infected grasshoppers at a temperature of 34 °C, rather than 40 °C, not only reduced survival rate (Fig. 2), but also impaired growth.

In the seven years that followed the first reliable report (Vaughn *et al.,* 1974) of fever in an ectotherm, sixteen other species of ectotherm were investigated (Kluger, 1986; Firth, Ralph and Boardman, 1980). Species studied included two other lizard species, five amphibian species, three fish species, and six species of arthropod; all exhibited pyrexia. Since fever was already known to occur in all mammals and birds that had been tested, a view began to prevail, explicitly or implicitly, that all animal species that had evolved with or since the arthropods could develop fever. If fever indeed was ubiquitous, that alone would be a powerful argument in favour of it having survival value (Kluger, 1979*a, b*). Moreover, if the pyrexia of fever can be shown to be advantageous to the host in the case of some species, it is tempting to extrapolate its survival value to all other species.

In 1981, we reported the consequences of injecting killed *A. hydrophila* on body temperature in the armadillo lizard *Cordylus cataphractus* (Laburn, Mitchell, Kenedi and Louw, 1981). It was the first report of a species failing to develop pyrexia in response to a pyrogen, and therefore suggested that fever was not ubiquitous. We have subsequently discovered a number of other species in which pyrexia does not occur. We report our data on other lizard species here, review the state of knowledge concerning fever in ectotherms, and also point out the particular contribution to the field of study of Namib Desert species. Some of our new data have been reported briefly to the International Congress of Physiological Sciences (Mitchell, Laburn and Matter, 1989).

FEVER IN INVERTEBRATES

Fever has been reported to develop in several species of arthropod, and more recently in an annelid. Within the arthropods, it was amongst the crustaceans that behavioural fever was first detected (Table 1). The freshwater crayfish *Cambarus bartoni,* given injections of killed *A. hydrophila,* selected warmer water, such that its selected body temperature rose almost 2 °C above the normal 22 °C (Casterlin and

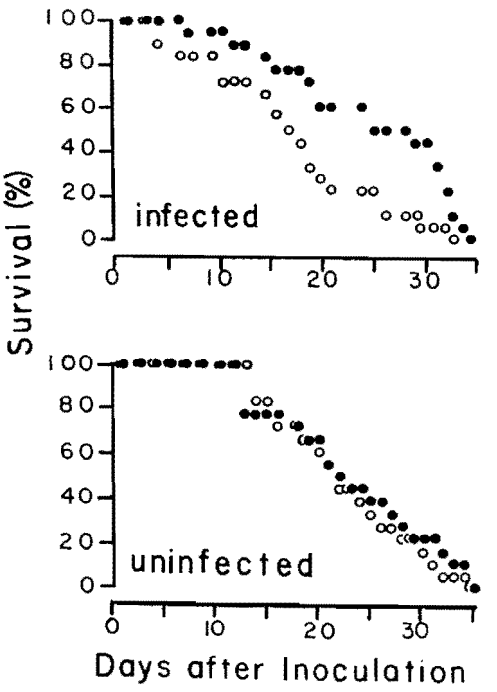

Fig. 2

Survival of the grasshopper *Melanoplus sanguinipes,* maintained at 34 °C (open circles) and 40 °C (closed circles), following ingestion of the live microsporidian protozoan *Nosema acridophagus* (top panel) or not infected (bottom panel). Maintaining the animals at 34 °C reduced survival rates significantly below the natural life expectancy curve. From Boorstein and Ewald (1987), by copyright permission of the University of Chicago Press.

Reynolds, 1977*b*). The pyrexial action of endogenous pyrogens, which are known to be released in invertebrates (Beck, Vasta, Marchalonis and Habicht, 1989) as in other animals during fever, is mediated in the nervous system of endotherms by eicosanoids, one of which is prostaglandin E (PGE) (Stitt, 1986; Mitchell, Laburn, Cooper, Hellon, Cranston and Townsend, 1986; Cooper, 1987; Hellon *et al.,* 1990). Injection of PGE into the central nervous system of vertebrates rapidly produces a potent pyrexia (Milton, 1982). Prostaglandins are released during inflammatory reactions in invertebrates too (Brady, 1983), but whether they mediate fever in ectotherms had not been tested. Systemic injection of PGE in *C. bartoni* evoked a behavioural fever (Casterlin and Reynolds, 1978); it also did so in two marine decapods, *Penaeus duorarum* and *Homarus americanus* (Casterlin and Reynolds, 1979). The aspirin-like drugs produce antipyresis by inhibiting eicosanoid synthesis (Dascombe, 1985), and dissolving one of these drugs, paracetamol (= acetominophen), in the water surrounding *C. bartoni* abolished the pyrexial response to *A. hydrophila* injection (Casterlin and Reynolds, 1980).

No specific survival value has been demonstrated for the pyrexia exhibited by crustaceans. However, as noted above, pyrexia does appear to benefit one of the insects, the grasshopper *Melanoplus sanguinipes,* during protozoal infection (Boorstein and Ewald, 1987). This grasshopper was not the

Table 1
Ectothermic species reported to develop fever when given pyrogens.

Species		Pyrogen	Reference
Invertebrates			
Nephelopsis obscura	(leech)	Endotoxin,PGE	Cabanac, 1989
Limulus polyphemus	(horseshoe crab)	PGE	Casterlin and Reynolds, 1979
Buthus occitanus	(scorpion)	PGE	Cabanac and Le Guelte, 1980
Androctonus australis	(scorpion)	PGE	Cabanac and Le Guelte, 1980
Gromphadorhina portentosa	(Madagascar cockroach)	Endotoxin, bacteria	Bronstein and Conner, 1984
Gryllus bimaculatus	(cricket)	Rickettsia	Louis *et al.*, 1986
Melanoplus sanguinipes	(migratory grasshopper)	Protozoa	Boorstein and Ewald, 1987
Onymacris plana	(tenebrionid beetle)	Endotoxin	McClain *et al.*, 1988
Cambarus bartoni	(freshwater crayfish)	Bacteria	Casterlin and Reynolds, 1977*b*
		PGE	Casterlin and Reynolds, 1978
Homarus americanus	(American lobster)	PGE	Casterlin and Reynolds, 1979
Penaeus duorarum	(pink shrimp)	PGE	Casterlin and Reynolds, 1979
Fish			
Micropterus salmoides	(largemouth bass)	Bacteria	Reynolds *et al.*, 1976
Lepomis macrochirus	(bluegill sunfish)	Bacteria	Reynolds *et al.*, 1976
Carassius auratus	(goldfish)	Bacteria, endotoxin	Reynolds *et al.*, 1978*b*
Amphibians			
Hyla cinerea	(green tree frog, adult)	Bacteria	Kluger, 1977
Rana pipiens	(leopard frog, tadpole)	Bacteria	Casterlin and Reynolds, 1977*a*
Rana catesbeiana	(bullfrog, tadpole)	Bacteria	Casterlin and Reynolds, 1977*a*
Rana esculenta	(edible frog, adult)	Bacteria, PGE, EP	Myhre *et al.*, 1977
Necturus maculosus	(mudpuppy)	PGE	Hutchinson and Erskine, 1981
Reptiles			
Dipsosaurus dorsalis	(desert iguana)	Bacteria	Vaughn *et al.*, 1974
		EP	Bernheim and Kluger, 1977
Iguana iguana	(green iguana)	Bacteria	Kluger, 1978
Crotaphytus collaris	(collared lizard)	Bacteria	Firth *et al.*, 1980
Saurimalus obesus	(chuckwalla)	Bacteria	Muchlinski *et al.*, 1989
Terrapene carolina	(eastern box turtle)	Bacteria	Monagas and Gatten, 1983
Chrysemys picta	(painted turtle)	Bacteria	Monagas and Gatten, 1983
Alligator mississippiensis	(American alligator)	Bacteria	Lang, 1986

first insect in which behavioural fever was observed; it had been reported previously in the Madagascar cockroach *Gromphadorhina portentosa* (Bronstein and Conner, 1984) and the cricket *Gryllus bimaculatus* (Louis, Jourdan and Cabanac, 1986). The cockroaches selected higher body temperatures when given injections of killed *E. coli,* another gram-negative bacterium, and of endotoxin, the lipopolysaccharide component of the cell wall that is considered to be the pyrogenic moeity of all gram-negative bacteria (Kenedi, Laburn, Mitchell and Ross, 1982). The crickets were infected with *Rickettsiella grylli,* thereby extending the range of pathogenic organisms tested to the rickettsials. The hosts not only selected higher body temperatures, but also survived better in thermal mosaics than they did at a fixed temperature equal to that of the uninfected animals (Louis *et al.*, 1986). Post-mortem examination of infected crickets showed exacerbation of the infectious process at lower body temperatures. The significance of Boorstein and Ewald's investigation of grasshoppers is that it was the first, and so far the only, report of a host benefiting from pyrexia when infected via a natural route, as the pathogenic protozoa were applied to the grasshoppers' food.

Until recently, the insect species in which fever has been reported were all members of the Orthoptera. The first demonstration of pyrexia in a non-orthopteran insect relied on a Namib Desert species, the tenebrionid beetle *Onymacris plana* (McClain, Magnuson and Warner, 1988). Namib tenebrionids are unusual amongst insects in that their selected body temperatures are high, falling in the mammalian range (Seely, Roberts and Mitchell, 1988). McClain and her colleagues placed adult *O. plana* in a photothermal gradient chamber. Injection of purified endotoxin into the haemocoel of the beetles resulted in their selecting a warmer position in the chamber (see Fig. 3); this behavioural pyrexia had an onset latency of less than an hour, and lasted about twelve hours.

The chelicerate arthropods are phylogenetically much older than the (mandibulate) insects, and demonstration of fever in chelicerates would suggest an ancient evolutionary origin of the phenomenon. Persistence of fever from an ancient origin to modern times again would be supportive of survival value. Such was the significance attached by Cabanac and Le Guelte (1980) to their discovery that PGE in doses between 1 and 5 mg/kg evoked behavioural pyrexia in the two scorpion species, *Buthus occitanus* and *Androctonus australis.* Both higher

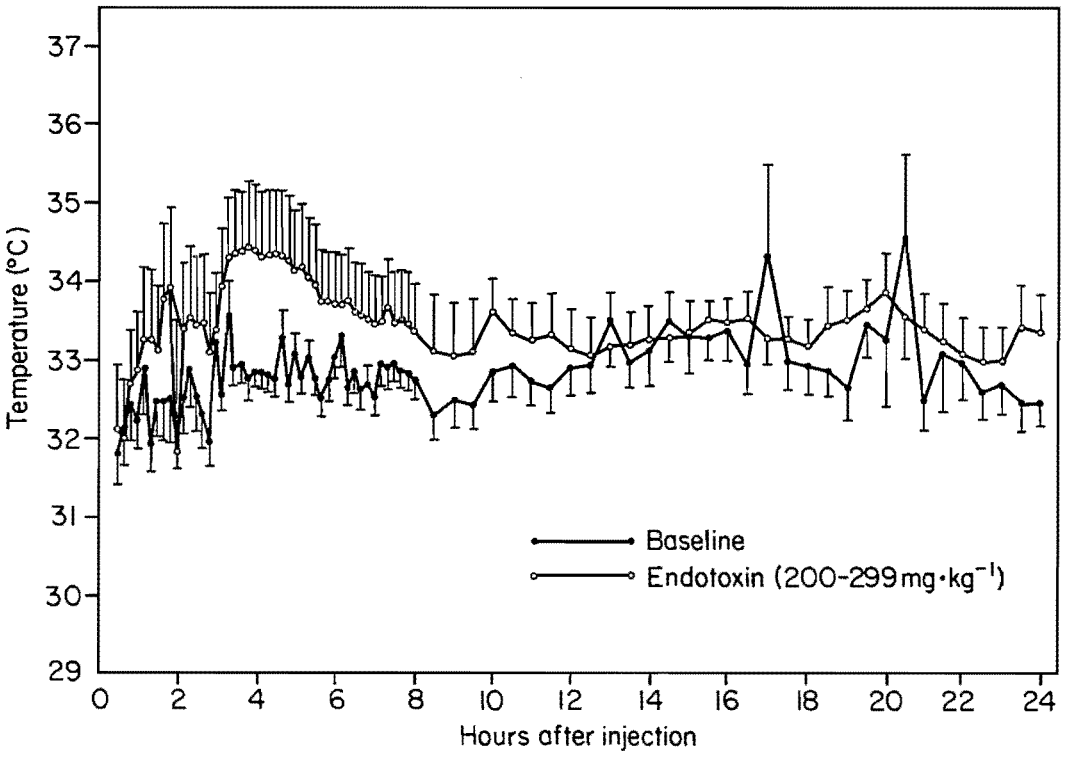

Fig. 3

Substrate temperatures selected by the Namib tenebrionid beetle *Onymacris plana*, maintained in a photothermal gradient chamber, with no intervention (closed circles) and following injection of purified endotoxin (open circles). Beetle thoracic temperatures were about 4 °C higher than substrate temperatures. From McClain, Magnuson and Warner (1988), by copyright permission of Pergamon Press.

and lower doses were without effect. The temperatures of the scorpions reached 40 °C, and the behavioural pyrexia in some individual scorpions lasted more than twenty hours. Another ancient chelicerate arthropod reported to develop behavioural fever is the horseshoe crab, *Limulus polyphemus* (Casterlin and Reynolds, 1979), which is more closely related to scorpions than to true crabs. Identification of fever in the chelicerates bestows on the phenomenon a potential evolutionary age of 300 million years (Cabanac and Le Guelte, 1980).

Three non-arthropod invertebrates have been tested for responsiveness to pyrogens, two snail species and a leech. The snails are the freshwater snail *Limnaea auricularia* (Cabanac and Rossetti, 1987) and the Japanese freshwater snail *Semisulcospira libertina* (Rossetti and Nagasaka, 1988). Challenged with either PGE or endotoxin, they failed to develop pyrexia (Table 2), a result the authors interpreted to mean that fever evolved after the molluscs diverged from the main evolutionary line, and before divergence of the arthropods. The study should be repeated with terrestrial snails, the habitats of which contain much richer thermal mosaics than those of aquatic snails.

The Annelida share a common divergence with the arthropods, and Cabanac (1989) recently has examined the responses of one of them, the leech *Nephelopsis obscura,* to endotoxin and prostaglandin injection. This leech did not take up a preferred position in an aquatic thermal gradient, but traversed both warmer and colder areas. The proportion of time spent in warmer areas increased following injection of bacterial endotoxin (0,25 mg/kg) and PGE (4 mg/kg). The preference for warmer water was abolished by paracetamol, dissolved in the water, in animals given 10 mg/kg of endotoxin; whether paracetamol had any effect on the thermal behaviour of control animals was not investigated.

FEVER IN FISH

Work that predated the studies of Vaughn and her colleagues (1974) by twenty years had established that fish survived viral infections better at warmer water temperatures than at cooler temperatures (Watson, Guenther and Rucker, 1954; Amend, 1970). However, the earlier workers had not investigated whether infection altered thermoregulatory behaviour in fish. Fish usually are exposed to less variation in ambient temperature than are terrestrial animals, and hence have less opportunity to develop behavioural pyrexia. Experimental investigation of fever in fish has relied on an aquatic shuttlebox for determining thermal preferences. The fish are able to swim between two chambers held at different temperatures, but cannot remain in any chamber, because their presence in the chamber is used to trigger heating or cooling of the surrounding water (Neill, Magnuson and Chipman, 1972). Behavioural fever was first reported in fish by Reynolds, Casterlin and

Table 2
Ectothermic species reported not to develop fever when given pyrogens.

Species		Pyrogen	Reference
Invertebrates			
Limnaea auricularia	(freshwater snail)	Endotoxin, PGE, EP	Cabanac and Rossetti, 1987
Semisulcospira libertina	(Japanese freshwater snail)	Endotoxin, PGE	Rossetti and Nagasaka, 1988
Fish			
Lepomis gibbosus	(pumpkinseed sunfish)	Endotoxin, PGE	Marx *et al.*, 1984
Reptiles			
Cordylus cataphractus	(armadillo lizard)	Bacteria, EP	Laburn *et al.*, 1981
Sceloporus occidentalis	(western fence lizard)	Protozoa	Schall and Sarni, 1987
Pachydactylus bibronii	(Bibron's gecko)	Bacteria, EP	present paper
Aporosaura anchietae	(shovel-snouted lizard)	Bacteria	present paper
Angolosaurus skoogi	(desert plated lizard)	Bacteria, endotoxin	present paper
Geochelone pardalis	(leopard tortoise)	Bacteria, endotoxin	Zurovsky *et al.*, 1987*c*
Psammophis phillipsii	(olive grass snake)	Bacteria, endotoxin	Zurovsky *et al.*, 1987*a*
Lamprophis fuliginosus	(brown house snake)	Endotoxin	Zurovsky *et al.*, 1987*a*

Covert (1976), who found that killed *A. hydrophila*, injected into the bluegill sunfish *Lepomis macrochirus* and largemouth bass *Micropterus salmoides*, caused a 1 °C to 3 °C increase in selected body temperature. Reynolds and his colleagues subsequently showed that *L. macrochirus* displayed behavioural pyrexia not only in response to the gram-negative bacterium *A. hydrophila* but also to the killed gram-positive bacterium *Staphylococcus aureus* (Reynolds, Casterlin and Covert, 1978). As mentioned previously, elevated body temperature, and reduced mortality also occurred in *Carassius auratus* infected with live *A. hydrophila* (Covert and Reynolds, 1977).

Another sunfish, the pumpkinseed sunfish *Lepomis gibbosus*, was investigated by Marx, Hilbig, and Rahmann (1984). In this species, endotoxin, injected intracranially, had no significant effect on selected body temperature. Intracranial injection of PGE produced a phenomenon that appeared to be pyrexia, but Marx and his colleagues demonstrated that the phenomenon actually was an artifact, caused by sedation of the fish and consequent passive heating. Their results raise the disturbing question of whether other pyrexias apparent after PGE injection (Table 1) might be confounded by the consequences of sedation, in those studies in which the apparatus used to test behavioural thermoregulation did not require the test animals to move in order to achieve and maintain a constant body temperature.

FEVER IN AMPHIBIANS

Aquatic shuttleboxes, used to investigate the action of pyrogens in fish, can be used equally well to study tadpoles. Intraperitoneal injection of killed *A. hydrophila* in tadpoles of the bullfrog *Rana catesbeiana* and the leopard frog *Rana pipiens* resulted in an increase of selected body temperature of almost 3 °C (Casterlin and Reynolds, 1977*a*). In adults of the green tree frog *Hyla cinerea*, an unusually good thermoregulator for an amphibian, injection of killed *A. hydrophila* resulted in selection of warmer positions in a damp thermal gradient chamber, such that body temperature increased about 2 °C, with an onset latency of 2–4 hours (Kluger, 1977). Adults of the edible frog *Rana esculenta* were tested in a similar gradient by Myhre, Cabanac and Myhre (1977). They found that two strains of mycobacterium, *Mycobacterium xenopi* and *M. ranae*, injected intraperitoneally, increased selected body temperature by about 6 °C, while a third strain, *M. aquae II*, had no effect. Myhre and colleagues explained this strain difference by pointing out that the first two strains were pathogenic in the frogs while the third was not; this argument seems spurious, however, since all the bacteria were killed before injection. In the same frogs, cross-transfusion of plasma from donor frogs, previously given *M. ranae* injections, induced pyrexia in recipients. Intracranial injection of PGE caused a marked hyperthermia, and death in two out of five animals.

Body temperature elevation in amphibians given PGE is not confined to frogs. It occurs too in a salamander, the mudpuppy *Necturus maculosus* (Hutchison and Erskine, 1981); intracranial injection of PGE resulted in a 5 °C rise in selected body temperature, to about 17 °C, sustained for at least 24 hours.

No specific survival value of fever has been demonstrated in amphibians.

FEVER IN REPTILES

It was in a reptile that ectothermic fever first was discovered and it is in reptiles that ectothermic fever has been investigated most thoroughly.

In the desert iguana *Dipsosaurus dorsalis*, killed and live gram-negative organisms cause a behavioural pyrexia with onset latency of 3–4 hours and duration of days (see Fig. 4) (Vaughn *et al.*, 1974; Kluger *et al.*, 1975). The behavioural fever can be abolished by antipyretic drugs (Bernheim and Kluger, 1976*b*). As noted previously, administration of the antipyretic drug compromised survival in infected lizards, as did confinement to afebrile body temperatures (Fig. 1).

Fever in *D. dorsalis* is not specific to one pathogenic organism. Intracardiac injection of two other bacteria, *Pasteurella*

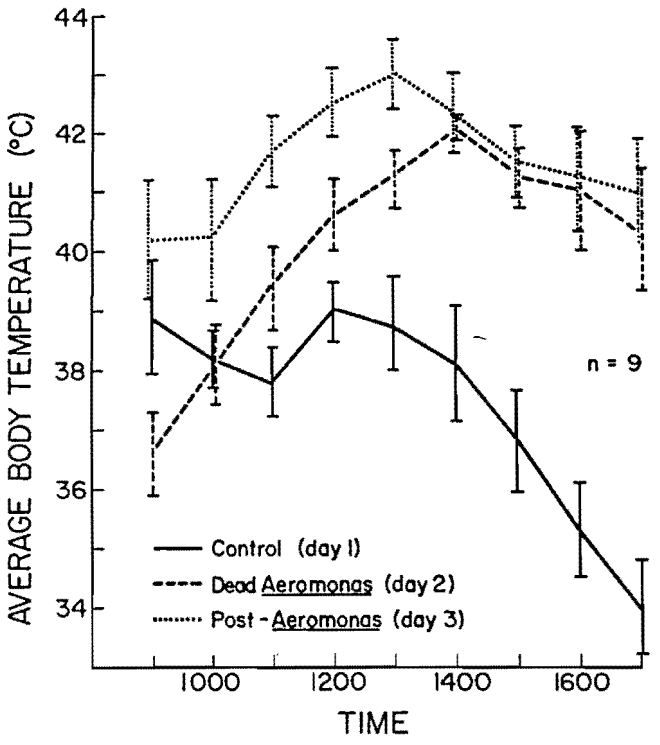

Fig. 4

Body temperatures of the desert iguana *Dipsosaurus dorsalis* in a photothermal gradient chamber, on a control day (Day 1), and on two days following intracardiac injection of the dead bacterium *Aeromonas hydrophila* at 09h00 on Day 2. From Bernheim and Kluger (1976*a*), by copyright permission of the American Physiological Society.

haemolytica (Kluger, 1978) and *Citrobacter diversus* (Kluger, 1979*a*), also resulted in elevation of selected body temperatures. The biochemical foundation of fever in *D. dorsalis* appears similar to that which prevails in mammals: peritoneal macrophages from the lizard synthesize EP *in vitro* (Bernheim and Kluger, 1977), and the lizards developed pyrexia both in response to this lizard EP and to rabbit EP. Components of fever other than pyrexia are displayed by *D. dorsalis* too: plasma concentrations of iron and zinc show the characteristic changes after injection of *A. hydrophila* (Hacker, Rothenburg and Kluger, 1981). The combination of elevated temperature and reduced iron concentration depressed the proliferation of *A. hydrophila in vitro* (Grieger and Kluger, 1978). Also, injecting iron into lizards along with live *A. hydrophila* compromised survival of the lizards (Grieger and Kluger, 1978). In infected lizards kept at their febrile temperature of 41 °C, granulocytes accumulated more rapidly at infection sites, and there was more rapid containment of the bacteraemia (Bernheim, Bodel, Askenase and Atkins, 1978). Serum antibody levels, and granulocyte chemotactic and phagocytic functions, were not improved, however.

Pyrexia following injection of killed *A. hydrophila* has been observed in three other lizard species, all members of the iguanid family. The second iguanid demonstrated to develop fever was the green iguana *Iguana iguana,* which exhibited behavioural pyrexia (Kluger 1978); there was no endothermic component (e.g., shivering, vasoconstriction) to its response (Malvin and Kluger, 1979). The third was the collared lizard *Crotaphytus collaris* (Firth *et al.,* 1980). More recently (Muchlinski, Stoutenburgh and Hogan, 1989), a fourth iguanid, the chuckwalla *Sauromalus obesus,* has been shown to elevate its selected body temperature at least 2 °C above its normal 36–40 °C, following *A. hydrophila* injection, not just in laboratory conditions but also in its natural habitat in the field. *S. obesus* fever was particularly evident on the second day after injection.

Pyrexia following pyrogen injections is not ubiquitous in lizards, however. We measured the body temperatures of the armadillo lizard *Cordylus cataphractus,* following intracardiac injections of the same dose of killed *A. hydrophila* that produced pyrexia in *D. dorsalis* (Laburn *et al.,* 1981). *C. cataphractus* is a cordylid lizard, with approximately the same body mass as *D. dorsalis;* it inhabits arid regions of southern Africa and is known for its sunbasking behaviour. It showed no change in selected body temperature after *A. hydrophila* injection, nor after injection of rabbit EP (Laburn *et al.*, 1981).

One possible explanation for the failure of *A. hydrophila* injection to cause fever in *C. cataphractus* is that the dose used was too high in this species (even though its mass was similar to that of *D. dorsalis*), and the lizard entered the equivalent of endotoxic shock. To check this possibility, we exposed *C. cataphractus* in the same photothermal gradient chamber, and injected $1/10$ and $1/100$ of the original dose: the selected body temperature following these lower doses of killed bacteria was the same as that which followed saline injection (Fig. 5).

Having demonstrated that at least one species of African lizard did not become pyrexic following pyrogen injection, we set out to investigate other species. *Pachydactylus bibronii* is a nocturnal gecko (mass approximately 14 g) which has widespread distribution throughout southern Africa. We constructed a thermal gradient chamber for the lizards by placing a glass flask containing water at one end of a terrarium, and controlling the temperature of the water at about 55 °C, too hot for the lizards to remain close to it permanently, using a thermostatically regulated immersion heater. We then conducted all measurements at night, in the dark. We measured the colonic temperature of the lizards using indwelling 36 gauge copper-constantan thermocouples, the outputs of which were connected to a data logger. Figure 6 shows the nocturnal body temperatures of lizards permanently resident in the terrarium. The average body temperature of the group of lizards, given saline, varied by only 1 °C over the night; the lizards were excellent thermoregulators. Interestingly, the selected body temperature was about 32 °C, very similar to that of *C. cataphractus,* and very much higher than the lizards ever could attain for most of the night in their natural habitats. Intracardiac injection of killed *A. hydrophila* had no effect on body temperature. In subsequent experiments, we injected 0,5 ml of a solution containing rabbit endogenous pyrogen, made according to the technique of Borsook, Laburn and Mitchell (1978) and tested for pyrogenicity in rabbits; it too had no effect on selected body temperature in *P. bibronii.*

The selected body temperatures of both *C. cataphractus* and *P. bibronii* were much lower than those exhibited by *D. dorsalis.* Iguanid lizards, as a family, generally select high body temperatures (Avery, 1979) close to the mammalian range.

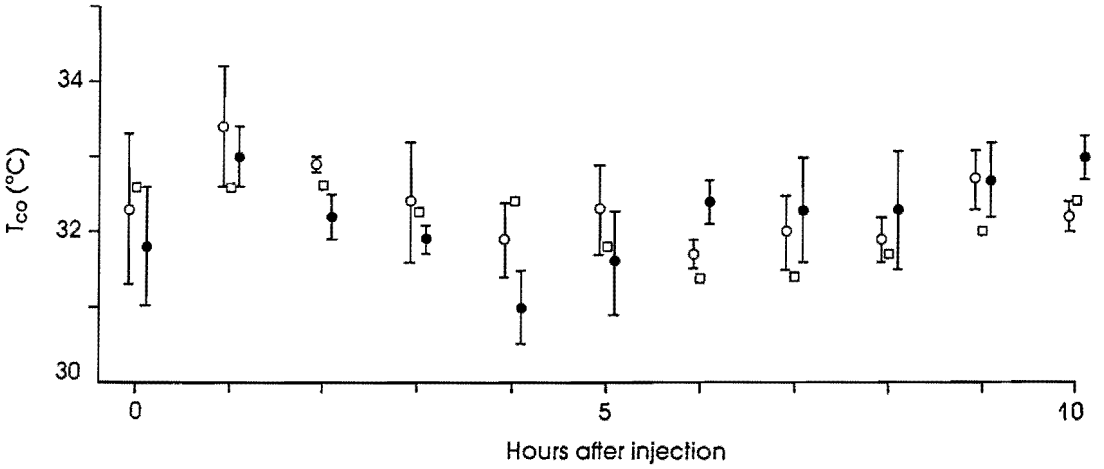

Fig. 5

Body temperatures (measured as colonic temperature, T_{co}) of armadillo lizards *Cordylus cataphractus* (mean ± *SE*, $n = 4$, mean mass = 60 g) in a photothermal gradient chamber. The direction of the thermal gradient in the chamber was reversed every 30 minutes, so that the animals had to thermoregulate actively, by changing position, to maintain a constant body temperature. At time zero, corresponding to 09h00, intracardiac injections were given, in random order, of 0,2 ml sterile saline (open circles), 4×10^7 killed organisms of *Aeromonas hydrophila* in 0,2 ml saline (squares) and 4×10^8 killed organisms in 0,2 ml saline (closed circles). Body temperatures did not differ significantly following the three treatments. These and all our other experiments were approved by the Animal Ethics Committee of the University of the Witwatersrand.

We considered it possible that fever occurred only in those species of lizards with a mammal-like body temperature. Such lizards had been reported from the Namib Desert (Hamilton and Coetzee, 1969), so we attempted to produce fever in two Namib species.

Aporosaura anchietae is a small (2–5 g) lacertid lizard, which inhabits sand dunes throughout the Namib (Louw and Holm, 1972). It is diurnally active, and present on the sand surface even when sand surface temperatures exceed 35 °C. As for most Namib dune species, the most obvious thermoregulatory behaviour available to *A. anchietae* is burying and emerging from the sand substrate. We captured *A. anchietae*

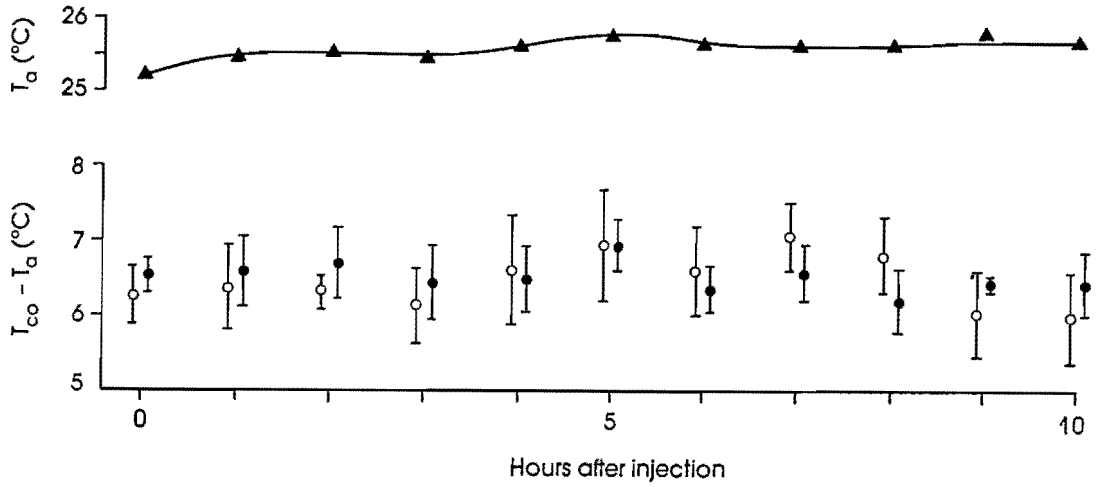

Fig. 6

Ambient temperature (T_a, triangles) and body temperature (measured as the difference between colonic temperature, T_{co}, and ambient temperature) of Bibron's gecko *Pachydactylus bibronii* (mean ± *SE*, $n = 6$, mean mass = 14 g), following intracardiac injection, in random order, of 0,2 ml sterile saline (open circles) or 0,2 ml saline containing 4×10^9 killed *Aeromonas hydrophila* (closed circles) at time zero, corresponding to 19h30. The measurements were carried out in the dark; a thermal gradient was obtained by including a glass flask of water thermostatically controlled at 55 °C in one corner of the terrarium. The lizards were permanently resident in the terrarium. Body temperatures did not differ following the two treatments.

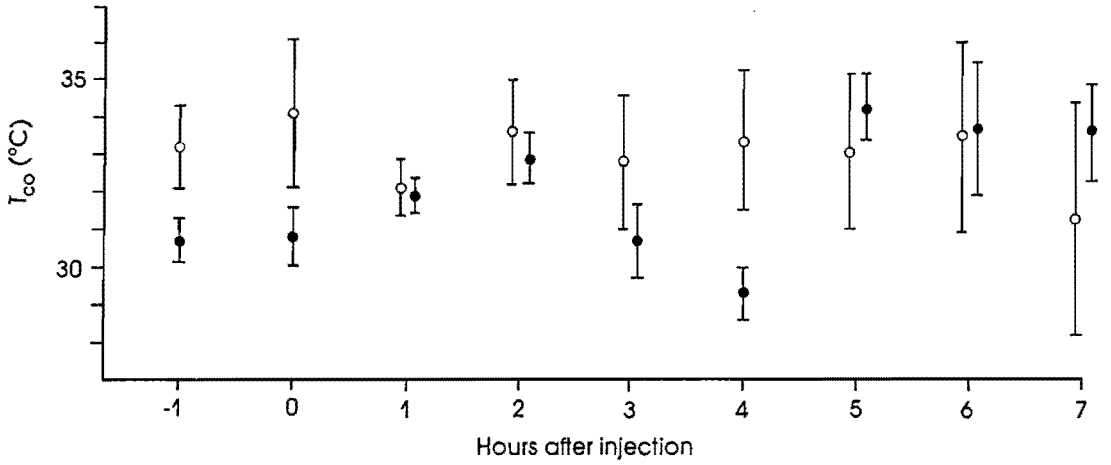

Fig. 7

Body temperature (measured as colonic temperature, T_{co}) of the shovel-snouted lizard *Aporosaura anchietae* (mean ± *SE*, $n = 5$, mean mass = 3 g), in a photothermal gradient chamber, given intracardiac injections, in random order, of 0,1 ml sterile saline (open circles) and 0,1 ml of saline containing 4×10^9 killed *Aeromonas hydrophila*. Body temperatures did not differ significantly between the two treatments.

on slipfaces in the central Namib dune sea near Gobabeb (23° 34′ S, 15° 03′ E) and placed them in a photothermal gradient chamber with a dune sand substrate and a tungsten lamp heat source. We measured colonic temperature using fine (36 gauge) copper-constantan thermocouples. Even this fine wire, when permanently attached, prevented the lizards from burying freely in the sand, so we did not use indwelling thermocouples but caught the lizards approximately every hour, and measured their colonic temperatures as rapidly as possible using a roving probe. Figure 7 shows that *A. anchietae* lizards showed considerable variability in body temperature, probably primarily because of their low thermal inertia, but that intracardiac injection of killed *A. hydrophila* had no effect on their selected body temperature. Moreover, all the lizards given killed *A. hydrophila* died within 12 hours of the injection, and none of those given intracardiac saline did; death following injection of killed bacteria in lizards has not been reported in other investigations of reptilian fever.

In our study, *A. anchietae* selected body temperatures closer to that of *C. cataphractus* and *P. bibronii* than to the mammal-like temperature of *D. dorsalis*. We therefore extended our investigation to another Namib dune lizard, *Angolosaurus skoogi*, a larger (up to 120 g) lizard, which is endemic to the northern Namib dune sea (Mitchell, Seely, Roberts, Pietruszka, McClain, Griffin and Yeaton, 1987). Like *C. cataphractus*, it is a cordylid lizard, and is capable of sophisticated thermoregulatory behaviour (Seely, Mitchell, Roberts and McClain, 1988; Seely, Mitchell and Goelst, 1990). We captured subadult *A. skoogi* on Skeleton Coast dunes near the Unjab River (20° 09′ S, 13° 14′ E) and placed them in an enclosure on a dune slipface, such that they were exposed to natural variations in microclimate, and were able to bury in the sand. We measured their colonic temperature with indwelling 36 gauge copper-constantan thermocouples. The thermocouples did impair movement somewhat, but the lizards nevertheless were able to bury and emerge, and to seek out different areas of the enclosure. At solar noon, we gave the lizards intraperitoneal injections either of saline or of a cocktail of pyrogens, containing both endotoxin and killed *Staphylococcus aureus*, and Fig. 8 shows the results. The lizards emerged from the sand at a time typical of their afternoon surface activity period, and attained a temperature near 36 °C, very similar to that of *D. dorsalis*. Unlike *D. dorsalis*, however, their selected body temperatures were unaffected by the injection of the pyrogen. We have therefore failed, so far, to find an African lizard which becomes pyrexic, though we have investigated four species in three families.

Indeed, we have failed to find any African reptile that becomes pyrexic. Apart from the four iguanid lizard species, three other reptile species have been reported to select higher body temperatures following injection of *A. hydrophila*. Two of these are turtles, *Terrapene carolina* and *Chrysemys picta* (Monagas and Gatten, 1983). The leopard tortoise *Geochelone pardalis*, widespread throughout southern Africa, selected a deep body temperature of 33 °C in a photothermal gradient chamber. This body temperature was not affected by killed *S. aureus*, killed *Salmonella minnesota*, nor by endotoxin (Zurovsky, Mitchell and Laburn, 1987). We also investigated two African snakes in the photothermal gradient chamber. The same spectrum of pyrogens failed to elicit a change in selected body temperature in the olive grass snake *Psammophis phillipsii*, which is diurnally active and a sunbasker, and endotoxin did not affect selected body temperature in the crepuscular to nocturnal brown house snake, *Lamprophis fuliginosus* (Zurovsky, Brain, Laburn and Mitchell, 1987).

The third non-iguanid reptile reported to develop fever following *A. hydrophila* injection is the American crocodilian *Alligator mississippiensis* (Lang, 1986). Young animals given

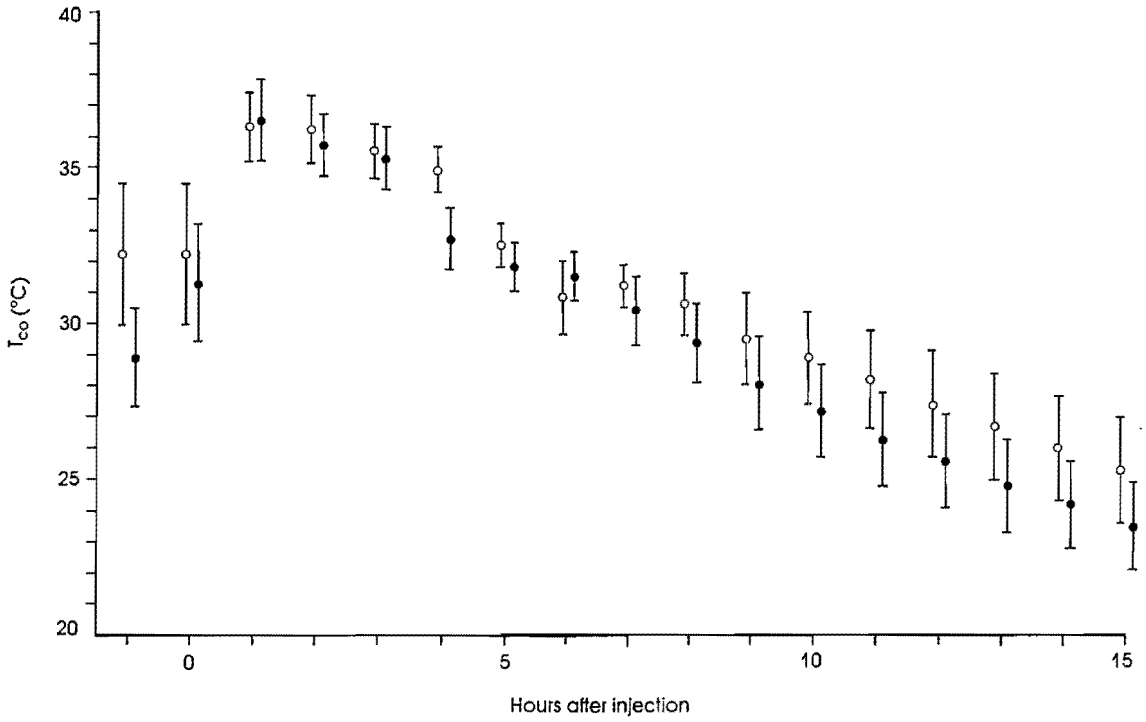

Fig. 8

Body temperatures (measured as colonic temperature, T_{co}) of the desert plated lizard *Angolosaurus skoogi* (mean ± *SE*, $n = 6$, mean mass = 60 g), following intraperitoneal injection, in random order, of 0,5 ml sterile saline (open circles) or 0,5 ml saline containing 4×10^9 killed gram-positive bacteria *Staphylococcus aureus*, and 10 µg/kg endotoxin (ex *Salmonella typhosa*, Difco) at time zero, corresponding to solar noon. Lizards were confined to an enclosure on a dune slipface, and exposed to the natural microclimate. All lizards had buried in the sand substrate within 6 hours of time zero. There were no significant differences in body temperature between the two treatments. The body temperatures of the lizards, in both cases, followed the pattern typical of animals that emerged on to the hot surface for a short period and then buried in the cooler sand for the rest of the day.

an unspecified dose of live bacteria selected warmer parts of a thermal gradient such that their body temperatures were elevated for 1–2 days, returning to normal after 3–4 days. It is difficult to know by how much the selected body temperature (normally 28–30 °C) was elevated, because the statistical analysis in Lang's paper appears to be invalid; he used 10 animals but reports a sample size between 30 and 120 in his analysis. In a previous experiment (Glassman and Bennett, 1978), the same species of alligator had been exposed to increasing doses of live *A. hydrophila* in their habitat water, while the water was was kept at constant temperatures between 20 °C and 35 °C. Host defence to the bacterial infection, as reflected in total leucocyte and neutrophilic macrophage concentrations, was optimum at a water temperature of 30 °C, close to the selected body temperatures of the animals when not infected. At a water temperature of 35 °C, all infected animals died whereas healthy animals survived: the pyrexia therefore did not appear to be beneficial.

In all the studies in which fever has been demonstrated in reptiles, the pyrogen has been injected into the host animal. Like other taxa, however, reptiles have naturally occurring infections of potentially pyrogenic microorganisms, and lizards are frequently hosts of *Plasmodium* protozoa (Schall, Bennett and Putnam, 1982). *Plasmodium falciparum* is a cause of malaria in humans, and malaria is characterized by recurring fever of very high amplitude. Another species, *Plasmodium mexicanum,* is very prevalent in northern California in an iguanid lizard, the western fence lizard *Sceloporus occidentalis*. It is very intriguing that infected *S. occidentalis* spend more time in the shade than do non-infected animals, and have a selected body temperature in both field and laboratory conditions which is not significantly different to that of healthy animals (Schall and Sarni, 1987). It is possible that *P. mexicanum* is not a pyrogenic organism; alternatively, fever is not ubiquitous even amongst iguanid lizards.

Of the fifteen species of reptile that have been investigated, therefore, pyrexia following pyrogen injections has been reported in seven: four species of lizard, all iguanids, two species of turtle, and one crocodilian.

FEVER AND SURVIVAL

We have attempted to assemble all the available data on fever in ectotherms. In evaluating whether the data supports the concept that fever has survival value, or, in other words, contributes to the biological fitness of a host, we need to address a number of questions. To what extent do the reported hyperthermias represent true pyrexias, and to what extent are they aberrations of thermoregulation? How well do the laboratory interventions mimic the natural events that might lead to

fever in the host? How do apparent benefits of the fever weigh up against costs? To what extent can one extrapolate from one host to another, and particularly, extrapolate from ectotherms to endotherms? How widely distributed is fever phylogenetically? We have already mentioned that the hyperthermia which follows PGE injection in invertebrates may sometimes be an artifact of sedation. High doses of PGE sedated scorpions (Cabanac and Le Guelte, 1980), and either sedated or killed snails (Cabanac and Rossetti, 1987). Systemic injection of PGE cannot be used to produce pyrexia in vertebrates, because the dose required would be toxic. To produce an elevation of body temperature in invertebrates by systemic injection of PGE required a very high dose, 4 mg/kg in scorpions and leeches, for example (Cabanac and Le Guelte, 1980; Cabanac, 1989). Injection of PGE into the central nervous system in nanogram doses per kilogram body mass, causes hyperthermia in endotherms.

Regardless of which pyrogen is involved, if an elevation in body temperature represents fever, rather than any other form of hyperthermia, then that elevation must have particular attributes. Specifically, the elevated body temperature in endotherms is defended in the face of environmental heat and cold stress. No-one appears to have devised an experiment to test quantitatively whether thermoregulation remains fully competent during the elevations of temperature that have been observed in ectotherms, following injections of pyrogens. Another attribute is that the temperature should be reduced by antipyretic drugs, an attribute which has been confirmed only for the leech *N. obscura* (Cabanac, 1989), the crayfish *C. bartoni* (Casterlin and Reynolds, 1980), the desert iguana *D. dorsalis* (Bernheim and Kluger, 1976*b*) and the bluegill sunfish *L. macrochirus* (Reynolds, 1977). Another requirement of pyrexia in ectotherms, if it reflects true fever, is that it should be accompanied by some, or all, of the other features of fever, such as release of acute-phase proteins, and changes in metallic ion concentration, as has been demonstrated in *D. dorsalis* (Hacker *et al.*, 1981), but not yet investigated in other ectothermic vertebrates. Whether or not the pyrexia contributes to survival, some of these other features indeed do so (Duff, 1986). Prostaglandins do not elicit the acute-phase response (Hellon *et al.*, 1990), so animals in which PGE has been injected, apart from the problems arising from dose, do not have the same repertoire of responses as those given the pyrogen of a pathogenic organism. Those species in which the only pyrogen that has been used is PGE need to be reinvestigated with other pyrogens. Indeed, apart from the peculiar problems associated with PGE, we believe that more than one pyrogen should be used whenever a species is tested for the existence of fever.

Almost all investigations of reactions of ectotherms to pyrogens have been carried out in artificial environments in laboratories. If the reactions are to be used to evaluate the survival value of fever, then the experimental conditions should simulate the natural environment as far as possible. For example, in the study of Cabanac and Le Guelte (1980) on scorpions in which the experimental chamber was 'uniformly and permanently illuminated', it would have been an improvement to conduct the study in the dark since both species of scorpion used are active only nocturnally in their natural habitat; the results would not necessarily be different, of course. In the study of McClain *et al.* (1988) on tenebrionid beetles, the beetles were prevented from using their most potent anti-hyperthermic behaviour, namely burying in the sand substrate. Similarly, the steep thermal gradients used to study aquatic animals in the laboratory are seldom, if ever, available to the animals in their natural habitats.

Even if one establishes that fever occurs in an ectotherm in a natural environment, it contributes positively to the fitness of the host only if its benefits outweigh its costs (Boorstein and Ewald, 1987). Low mortality in the presence of fever following a pathological event, and high mortality in its absence following the same event, would be a cogent argument for a positive survival value, but such an outcome has not yet been demonstrated for any species in a natural environment. In our opinion, the closest approximation is the study on the grasshopper *M. sanguinipes* by Boorstein and Ewald (1987). The lizards with naturally acquired malaria did not develop fever (Schall and Sarni, 1987). At the organ and cellular level, there are many mechanisms which one predicts would favour host survival better in febrile than in afebrile conditions (see Kluger, 1986; Dinarello *et al.*, 1986; Roberts, 1979), but whether they are specific and successful survival mechanisms requires direct proof in a living organism. It is noteworthy, for example, that the combination of high body temperature and low serum iron concentration, which presents a hostile environment to some species of gram-negative bacteria and therefore ought to benefit a host (Kluger and Rothenburg, 1979), does not occur in baboons given gram-negative pyrogens (Zurovsky, Laburn, Mitchell and MacPhail, 1987), and does occur in humans in a hyperthermic situation other than fever, where it has no obvious survival value, namely exercise (Taylor, Rogers, Goodman, Baynes, Bothwell, Bezwoda, Kramer and Hattingh, 1987).

There are undoubtedly costs associated with fever too. The energy cost of pyrexia *per se* is particularly high in ectotherms (Muchlinski, 1985). In addition, several biochemical and physiological events occur in fever in both ectotherms and endotherms which appear to compromise the host and therefore should be considered as costs; they include inactivity, lack of appetite, loss of mass, nervous system malfunction and dehydration (Roberts, 1979; Blatteis, 1986; Boorstein and Ewald, 1987). In some laboratory studies using endotherms, pyrexia has been shown actually to increase mortality (Banet, 1986). Indeed, Banet (1983) believes that the stimulation of the immune system by pyrogens benefits the host, but the concurrent pyrexia is counteradaptive; fever without pyrexia, which may well occur in many ectotherms, would be more advantageous to the host than fever with pyrexia. Such a view would be consistent with the observations of Glassman and Bennett (1978) that elevation of the body temperature of alligators to 35 °C during an infection increased mortality; their defence mechanisms are optimally active at their afebrile selected temperature of 30 °C.

If assessments of the cost : benefit ratios in a sample of species are to be used to derive general principles, then one must consider whether interspecific extrapolations are valid. In particular, extrapolations from ectotherms to endotherms are precarious. Because the temperatures of ectotherms can vary over a relatively large range, there is a concomitant large variation in the rate of biochemical processes, and depression

of such processes at febrile temperatures in infected ectotherms may well limit the host's ability to mount defences through a non-specific Q10 effect (Muchlinski, 1985); in endotherms, however, the difference between febrile and afebrile temperatures is much less. (Indeed, the studies showing improved survival of infected ectotherms at high body temperatures should be repeated with pathogenic organisms that do not cause marked elevations in body temperature.) Also, endotherms generally appear to be more sensitive to exogenous pyrogens than are ectotherms, though there is a wide variation in sensitivity amongst endotherms and amongst ectotherms. The same absolute dose of killed *A. hydrophila* that will induce a 2 °C rise in body temperature in the lizard *D. dorsalis* of mass 25–60 g (Bernheim and Kluger, 1976*a*) will do the same in 3 kg rabbits (Laburn *et al.*, 1981), which are particularly sensitive to endotoxin; mass-specific sensitivity therefore differs by two orders of magnitude. The dose of endotoxin required to elevate selected temperature in *O. plana* beetles (McClain *et al.*, 1988) was more than a million times the pyrogenic dose of the same endotoxin in rabbits (Warner, Mitchell, Savage and McClain, 1985).

Notwithstanding differences in sensitivity to pyrogens, the mere existence of fever in phylogenetically disparate species is a persuasive argument in favour of it benefiting the host. The argument was most cogent when all species tested, including all ectotherms, appeared to respond to pyrogens. We now know that fever is not ubiquitous amongst ectotherms; of the 37 species investigated so far, 11 have shown no response to pyrogens (Tables 1 and 2). Of the 26 showing a response, 6 have been tested only with PGE. We know now that there are endothermic species, and particularly primates, highly resistant to pyrogens (Zurovsky *et al.*, 1987*b*). Also, there are circumstances in which the responses to pyrogens are suppressed in normally sensitive endotherms. One is parturition, where fever may be suppressed in both mother and neonate (Cooper 1987; Hellon *et al.*, 1990). Another is malnutrition (Hoffman-Goetz and Kluger, 1979; Hoffman-Goetz, McFarlane, Bistrian and Blackburn, 1981), a circumstance in which compromised resistance to infection can be fatal.

So fever is neither a ubiquitous nor a consistent response to pyrogens, and the question of why it occurs, when it does occur, remains unanswered. Further studies of Namib and other ectotherms may help solve the problem. For example, it may be coincidence, or it may be phylogenetically important, that four out of five iguanid lizard species tested so far have responded to pyrogens, but no lizards from other families have done so, even when the species have evolved in very similar desert habitats. Also, very few ectotherms have been tested for non-thermal responses to pyrogens. It is possible that the thermal and non-thermal components of fever have evolved separately; in *Dipsosaurus dorsalis* the fall in serum iron concentration which follows administration of bacteria is independent of changes in body temperature (Grieger and Kluger, 1978). If the non-thermal components have more survival value than the thermal component, the non-thermal components may well be present even in the absence of pyrexia, and pyrexia, when it occurs, may be incidental.

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