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The Evolution and Adaptive Value of Fever

Long regarded as a harmful by-product of infection, fever may instead be an ancient ally against disease, enhancing resistance and increasing chances of survival

Fever is a frequently treated symptom of many disease states. Attempts to lower body temperature during a febrile episode, whether through drugs such as aspirin or physical means such as sponge baths, are based on the assumption that fever is a harmful by-product of infection—that is, that fever is maladaptive. This assumption may not be valid. When Bennett and Nicastri (1960) reviewed the question of whether fever had a harmful effect on the infected host, they were unable to draw definitive conclusions. The role of fever in disease remained an enigma. A more recent survey of work on fever (Atkins and Bodel 1972) also raised the question of its function and concluded that there was no strong evidence that fever was either beneficial or harmful.

Several years ago I became interested in the question of the part played by fever in disease. One possible way to explore this question would be to infect two groups of mammals with a dose of pathogenic bacteria virulent enough to kill about 50 percent of the animals. One group would be allowed to develop a normal fever, while the other would be prevented from doing so. The mortality rates for the two groups could then be compared. The problem with such an experiment is that it is very difficult to prevent a rise in body temperature in a group of infected mammals without affecting the results.

For example, one way to prevent a fever would be to administer antipyretic drugs. But having done this, we could not be certain whether differences in mortality, if any, were due to the reduction in temperature itself or to some other side effect of the drugs. We could also prevent an elevation in body temperature by exposing one group of animals to an extremely low ambient temperature, while allowing the other group to remain at normal external temperatures. But again, differences in mortality could be attributed either to the differences in body temperature in themselves or to some side effect resulting from severe exposure to cold (e.g. raised plasma levels of cortisol, thyroxin, epinephrine, renin, and possibly other hormones).

It occurred to me that this problem might be resolved by selecting the proper animal species for study. If we could find an animal that would develop a fever in response to infection and yet at the same time could be prevented from doing so by some simple, relatively nonstressful means, we would have a suitable animal model to use in our investigations. A. V. Hill has been quoted as saying, "By the method of comparative physiology or of experimental biology, by the proper choice of a suitable organ, tissue or process, in some animal far removed in evolution we may often throw light upon some function or process in the higher animals or man" (Ratliff 1967). We felt that this comparative biological approach could be fruitful. The question was, what animal met the special conditions necessary for our investigations?

Endotherms and ectotherms

Thermal biologists divide vertebrates into two general groups, endotherms and ectotherms. The endotherms are those classes of vertebrates that have the capacity, as a result of metabolic processes, to generate sufficient internal heat to regulate their body temperatures (over a relatively narrow range of environmental temperatures) independently of external temperature. Mammals and birds are endotherms. Ectotherms lack the ability to generate sufficient heat internally and must rely on external sources of heat to regulate their body temperatures. With few exceptions, reptiles, amphibians, and fishes are ectotherms. Under natural conditions, endotherms and many ectotherms regulate their body temperatures within fairly narrow ranges. An ectotherm is capable of such regulation in the wild, since what appears to be a fairly uniform thermal environment generally consists of a vast array of thermal microhabitats. The ectotherm selects a "preferred" thermal environment and soon adjusts its body temperature to approximately that of its surroundings. In the laboratory, at normal room temperatures, most endotherms can still maintain a high and fairly constant body temperature. By contrast, an ectotherm's body temperature soon falls to room temperature in these artificial conditions. Since the body temperature of an ectotherm can so easily be manipulated, it occurred to us that an ectotherm might be a suitable model to use in our studies of the role of fever in disease.

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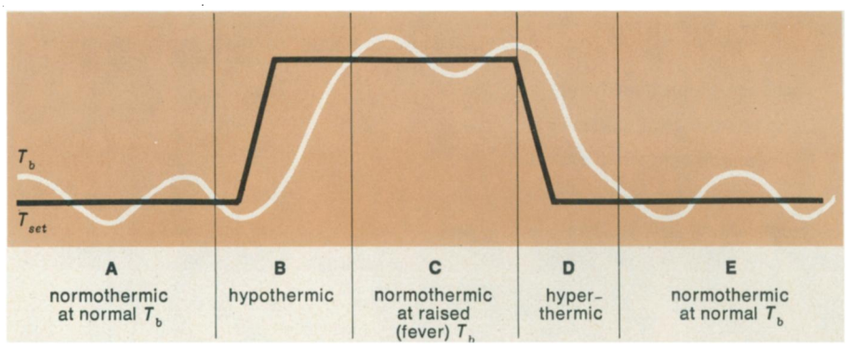

Figure 1. A diagrammatic representation shows the relation between body temperature (T_b) and set-point temperature (T_{set}) at various stages: (A) before the onset of fever, when T_b and T_{set} are approximately equal; (B) during the rising phase of fever; (C) during maintained fever; (D) during the subsiding phase; and (E) after return to normal thermoregulation. (From Bligh 1973.)

But the critical question remained: Do ectotherms develop a fever in response to infection? At the time we began our investigations, the only group of vertebrates conclusively shown to develop a fever following infection was the mammals. We suspected that birds as well as ectotherms (reptiles, amphibians, and fishes) would develop fevers under such conditions. The reasoning behind this assumption is described in detail below.

How temperature is regulated

The regulation of body temperature is governed by three general components of a reflex arc: sensors, integrators, and effectors. The sensors are capable of sensing temperature and converting this stimulus into appropriate patterns and frequencies of action potentials along the afferent or sensory nerves. Temperature sensors have been found in the skin as well as in internal structures such as the hypothalamus (a phylogenetically old structure in the forebrain), spinal cord, and abdomen. The integration of thermal responses is thought to occur to some extent in the hypothalamus, with some integrative abilities residing in other areas of the central nervous system. Here all the thermal input from the various sensors is somehow "weighed" and the appropriate efferent information is then passed on via nerves and hormones to the effectors, those structures that actually initiate the raising or lowering of body temperature.

For example, when an endotherm is exposed to a cold environment, signals are generated in thermal sensors in the skin that lead toward the hypothalamus and other areas involved in integration. In the integrator the thermal input from the cold skin and that from the neutral or even warm core are "weighed," and if the magnitude of the input from the skin is sufficiently great, efferent signals are sent to the skeletal muscles to initiate shivering (resulting in increased heat production), to the blood vessels of the skin to decrease blood flow to the skin (resulting in decreased heat loss), to the appropriate areas of the brain to initiate behavioral responses, such as putting on a sweater or seeking a warmer environment (resulting in decreased heat loss), and to many other thermoregulatory effectors as well.

The effector responses of ectotherms, which are primarily behavioral responses leading to the selection of a warmer or cooler microclimate, tend to be more limited. The comparative physiology of vertebrate thermoregulation has been reviewed many times in the past few years (see, e.g. Bligh 1973; Whittow 1970; Precht et al. 1973). It is readily apparent that the major difference between endotherms and ectotherms is found in the effector portion of the reflex arc. The sensory and integrating portions of this reflex are remarkably similar. The studies cited, involving localized warming or cooling, lesioning or ablating of neural tissue, and neurophysiological recordings, all demonstrate that the hypothalamus plays an important role in temperature sensation and integration in both endotherms and ectotherms. Temperature input to the hypothalamus from the skin and from extrahypothalamic deep body areas has also been shown to influence the effector responses greatly. Data such as these lead us to conclude that the neural control of temperature regulation in different vertebrate classes is very similar and probably has a common phylogeny.

Investigations of mammals have shown that a fever is not due to a failure of the mammal to regulate its body temperature, but rather is an actual resetting upward of the organism's temperature "set-point," or threshold for the activation of thermal responses (Cooper et al. 1964). Based on this "set-point" theory of regulation, Snell and Atkins (1968) have classified body temperatures into four useful categories. These are, briefly, (1) normothermia, where set-point and actual deep body temperature are essentially the same (occurs most of the time); (2) hypothermia, where set-point is normal but actual body temperature is reduced (can occur in response to disease, drugs, or exposure to cold); (3) hyperthermia, where set-point is normal but actual body temperature is higher (can occur in response to disease, drugs, or exposure to heat); and (4) fever, where set-point is raised and deep body temperature may or may not be raised to the same level.

Bligh (1973) has diagrammed these various states of body temperature, showing the change in set-point and the resulting body temperature as an individual goes from normothermia to fever and back again to normothermia (Fig. 1). In response to some infection, the T_{set} is raised and the individual develops a fever. Since T_b is less than T_{set}, the individual is hypothermic. Accordingly, all the effector mechanisms that will elevate T_b are initiated. For example, the individual increases metabolic heat production, decreases heat loss by decreasing skin blood flow and evaporative heat loss, and also employs behavioral responses which lead to a raised T_b. In man, these behavioral responses may include raising the temperature of the room, drinking hot liquids, putting on warmer clothing or blankets, and assuming postures that decrease heat loss. Once T_b equals T_{set} the individual is once again normothermic, though still fe-

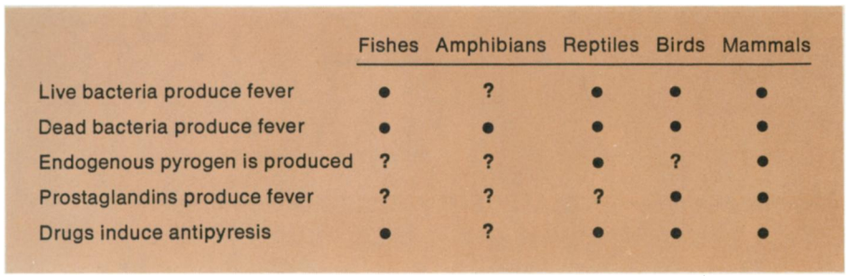

Figure 2. Febrile responses of mammalian and nonmammalian vertebrates are shown. Solid dots mark positive response; question marks indicate characteristics not yet tested.

brile. When the fever "breaks," T_{set} returns to its original level; however, T_b is now considerably above T_{set}. The individual is now hyperthermic and as such initiates responses, familiar to us all, which lead to a reduction in body temperature. There is an increase in flow of blood to the skin, an increase in evaporative heat loss (sweating), a reduction in metabolic heat production, and, again, many behavioral responses such as lowering room temperature, drinking cold liquids, and so on. When as a result of these strategies T_b again equals T_{set}, the individual is once more normothermic.

The actual mechanism by which the set-point is raised during fever is unclear. What is known is that in response to some activating agent (e.g. live bacteria, dead bacteria containing the cell wall or endotoxin, viruses), the host's leukocytes, and perhaps some other types of phagocytic cells, release a protein called endogenous pyrogen into the extracellular fluid. Endogenous pyrogen affects the hypothalamic temperature sensors and/or integrating neurons as well as other areas of the central nervous system, leading to a rise in T_{set}. How it does this is currently the subject of intensive investigation by many laboratories. The theory that some prostaglandin, perhaps PGE_1, is involved in fever has received a great deal of attention over the past few years. Prostaglandins are a group of physiologically active lipid soluble acids found in almost every tissue and body fluid (Goodman and Gilman 1975). Because of their numerous and diverse effects on the cardiovascular system, gastrointestinal secretions, smooth muscles, and other aspects of the body, they have attracted interest in many areas of biology. Some of the salient data supporting the prostaglandin theory of fever development are (1) injections of minute amounts of PGE_1 into the hypothalamus lead to a fever with a very short latency (Stitt 1973); (2) following inoculation with endotoxin (Feldberg and Gupta 1973) or with endogenous pyrogen (Cranston et al. 1975), prostaglandin activity increases in the cerebrospinal fluid, suggesting increased brain synthesis or release; (3) antipyretic drugs such as indomethacin or aspirin have been shown to inhibit prostaglandin synthesis (Vane 1971).

There are also strong arguments against the role of prostaglandin in pyrogen-induced fever. For example, Stitt and Hardy (1975) have shown that microinjections of PGE_1 onto temperature-sensitive neurons in the hypothalamus have little effect on their firing rates. However, these results are not in accord with the findings of several other investigators (Wit and Wang 1968; Cabanac et al. 1968; Eisenman 1969), who have shown that systemic injections of bacterial pyrogens led to changes in the firing rates, or thermosensitivity, of these neurons. A fascinating study of rabbits by Cranston et al. (1975) suggests that when prostaglandin synthesis is blocked by infusion of sodium salicylate, injections of endogenous pyrogen still lead to the development of fever. Several other studies along these same lines (Veale and Cooper 1975; Sanner 1974; Cranston et al. 1977) also raise the question of the significance of prostaglandin fevers. It appears, therefore, that prostaglandin fevers can be dissociated from pyrogen-induced fevers. Since many inflammatory processes lead to increased prostaglandin levels (see Goodman and Gilman 1975), prostaglandin might be an alternate pyrogenic substance which works directly on some hypothalamic area (perhaps the integrating area) distinct from the neurons affected by endogenous pyrogen.

Regardless of the specific biochemical and neural events occurring in the hypothalamus and other areas of the central nervous system, the infected organism behaves as though its thermostat setting has been elevated, and as a result actively uses both physiological and behavioral effector mechanisms to raise body temperature. Since the sensory-integrator component of the thermoregulatory reflex in different classes of vertebrates is so similar, and since it is this component that is affected by pyrogens in mammals, we suspected that nonmammalian vertebrates would also develop a fever in response to infection, and we initiated a series of systematic investigations to determine whether this was so.

Evolution of fever

If mammalian fever had its origin in the nonmammalian vertebrates, then the general characteristics of fever should be similar for all vertebrates. Briefly, some salient characteristics of mammalian fever are (1) inoculation of an organism with live pathogenic bacteria or viruses results in a fever; (2) inoculation of an organism with dead bacteria containing the endotoxin results in a fever; (3)in response to some activator (bacteria, viruses, etc.), the host's leukocytes produce endogenous pyrogen; (4) injections of prostaglandins into the hypothalamus produce a fever; (5) drugs such as sodium salicylate (aspirin) and acetaminophen attenuate or abolish a fever. If fever indeed has a common phylogeny in both mammals and nonmammals, these responses should be found in nonmammalian vertebrates as well. The findings for birds, reptiles, amphibians, and fishes summarized here (Fig. 2) strongly suggest that this is the case.

Birds were found to exhibit four of the five characteristics of mammalian fever listed above (the fifth has not yet been tested). Pigeons developed a fever following injection of live pathogenic bacteria (D'Alecy and Kluger 1975). Injection of dead bacteria containing endotoxin resulted in fever in both chickens and pigeons (van Miert and Frens 1968; D'Alecy

and Kluger 1975). Unlike laboratory animals, which exhibit fever when injected systemically with endotoxin, birds seem to respond with an initial fall in body temperature (Pittman et al. 1976; D'Alecy and Kluger 1975). This initial "cryogenic" response is followed by a dose-related fever in pigeons. Injections of prostaglandins directly into the hypothalamus of birds (Pittman et al. 1976) produce a fever of short latency. Sodium salicylate given orally results in effective antipyresis in bacterially infected pigeons (D'Alecy and Kluger 1975).

The responses of reptiles were tested by placing desert iguanas (*Dipsosaurus dorsalis*) in a chamber in which the temperature was held at about 50°C at one end and 30°C at the other. To maintain their preferred body temperature of about 38°C (Kluger et al. 1973), the lizards shuttled back and forth between the hot and cold sides of the chamber. Injection of these lizards with *Aeromonas hydrophila,* a bacterium pathogenic to reptiles, amphibians, and fishes, led to the lizards' behaviorally selecting a warmer body temperature by spending more time at the warmer end of the chamber (Vaughn et al. 1974). This elevation of the lizards' body temperature was clearly the result of a resetting of the "thermostat" within the central nervous system, since the lizards actively raised their body temperatures by choosing to spend more time in the heat. Further studies performed in a simulated desert environment have shown that both desert iguanas and green iguanas (*Iguana iguana*) will respond to injection of dead or live bacteria (both *A. hydrophila* and *Pasteurella haemolytica*) by developing a fever (Kluger, unpub.) (Fig. 3). Sodium salicylate attenuates the fever produced by bacterial pyrogens (Bernheim and Kluger 1976a).

By slightly modifying methods used to isolate endogenous pyrogen in mammals, we were able to isolate an endogenous pyrogen-like protein in desert iguanas (Bernheim and Kluger 1977), which when injected into other lizards produced a fever. However, when the endogenous pyrogen was heated to about 90°C the fever-producing activity ceased. Endogenous pyrogen isolated from rabbits will also produce a fever when injected into either rabbits or lizards, and again, heating the substance destroys its ability to produce fever in either animal.

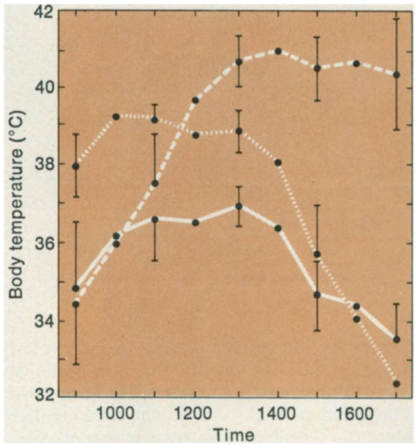

Figure 3. Body temperatures of seven green iguanas (*I. iguana*) are recorded by day and hour. The solid line indicates Day 1, the control. On Day 2 (dashed line) each lizard received an intracardiac injection of 0.2 ml of 2 × 10^{10} dead *A. hydrophila* at 0900 hr. The lizards developed a behavioral fever beginning about three hours after the injection and lasting until about 1500 hr on Day 3 (dotted line). (The vertical bars = 1 SEM.)

Both amphibians and fishes also share febrile characteristics with mammals. In amphibians, it has been established that injections of *A. hydrophila* into adult tree frogs (*Hyla cinerea*) (Kluger et al. 1977; Kluger 1977) or into tadpoles of bullfrogs and leopard frogs (*Rana catesbeiana* and *R. pipiens*) (Casterlin and Reynolds 1977) result in behavioral fevers. Injections of *A. hydrophila* into several species of fishes also lead to behavioral fevers, and it has been demonstrated that the drug acetaminophen produces effective antipyresis in fish (Reynolds et al. 1976; Reynolds and Covert 1977).

Since this comparison of febrile responses reveals that the characteristics of fever among the various vertebrate classes are remarkably similar, it follows that nonmammals as well as mammals might make suitable subjects for investigation of the role of fever in disease.

Adaptive value of fever

As suggested earlier, the ideal animal for such a study would be one that developed a fever in response to infection, yet at the same time could easily be prevented by some relatively nonstressful means from elevating its body temperature. An ectotherm or behavioral thermoregulator such as the desert iguana is just such an animal. We infected desert iguanas with live *A. hydrophila* and then held them in incubators at 38°C (their normal afebrile body temperature), at 40 and 42°C (body temperatures equivalent to the elevated set-point temperatures during low and high fevers, respectively), and at 34 and 36°C (hypothermic temperatures). There was a positive correlation between the lizards' temperatures and the survival rate in these bacterially infected animals (Kluger et al. 1975) (Fig. 4).

In a subsequent experiment, desert iguanas were allowed to regulate their body temperatures in a simulated desert environment (Bernheim and Kluger 1976b). Following infection with the same dose of live *A. hydrophila* that killed 75 percent of the lizards held at 38°C, these lizards developed fevers and behaviorally selected a body temperature of about 41°C during the day. At night, when room temperature fell to about 12°C, the lizards' body temperatures were also at approximately 12°C. Of the 12 febrile lizards, only 1 (or 8 percent) died.

These data supported our earlier work and demonstrated that the beneficial effects of an elevated body temperature occur under these more natural conditions where body temperature remains elevated only during the daytime. Antipyresis of this fever using sodium salicylate led to mortality in 7 of 7 animals. When 8 additional lizards were given the same dose of antipyretic drugs, yet prevented from lowering their body temperature (by keeping them in a constant-temperature incubator), only 1 died (12 percent). This indicated that the increased mortality following the administration of sodium salicylate to bacterially infected animals was due not to some side effect of the drug but rather to the reduction in body temperature itself.

Covert and Reynolds have also shown (1977) that survival of bacterially infected goldfish (*Carassius auratus*) is related to their body temperature. Infected goldfish will select a water temperature of approximately 31°C, 2 to 3°C above their normal afebrile

body temperature of about 28°C. Maintenance of infected goldfish at a temperature at or below 28°C leads to greater mortality, compared to the febrile fish at 31°C.

These studies demonstrate that fever during bacterial infection leads to decreases in mortality in a reptile and a fish. A fever in response to a bacterial infection with *A. hydrophila* clearly has an adaptive role in these organisms. Whether this is a general beneficial effect characterizing infection with other pathogens is not yet known. It is also unknown whether these results can be extrapolated to endothermic vertebrates—birds and mammals. Since the data on febrile responses throughout the vertebrates are so similar, we hypothesized that the survival of bacterially infected birds and mammals would also be related to the magnitude of their fever (Kluger et al. 1975; D'Alecy and Kluger 1975; Bernheim and Kluger 1976b).

The question of whether fever has survival value in mammals has been investigated using the New Zealand white rabbit (*Oryctolagus cuniculus*). Rabbits were infected with *Pasteurella multocida*, a common pathogen of rabbits, and the resulting fevers were correlated with the survival rate (Vaughn and Kluger 1977). An increase in the percentage of rabbits surviving the infection was found as the magnitude of the fever increased to approximately 2.25°C (Vaughn, 1977 diss.). Above a fever of 2.25°C, the mortality rate increased. These data are clearly correlative and demonstrate no causal relationship; however, if there is a causal relation between fever and survival in these bacterially infected mammals, then clearly there is some optimum range, with fevers above and below it leading to increased mortality. We conclude that these data support the hypothesis that moderate fevers in bacterially infected mammals are beneficial to the infected host.

Host defense mechanisms

The specific mechanisms behind the adaptive value of fever are currently under investigation. Earlier (Kluger et al. 1975) we speculated that several components of the defense mechanisms might be enhanced by increased temperature, including phagocytic index, phagocyte bactericidal activity, leukocyte mobilization, and humoral mediation of inflammation. Bernheim et al. (1977) have recently reported that fever in lizards does increase the mobility of leukocytes to the site of infection. No differences were observed in agglutinating antibody titers between febrile and afebrile animals.

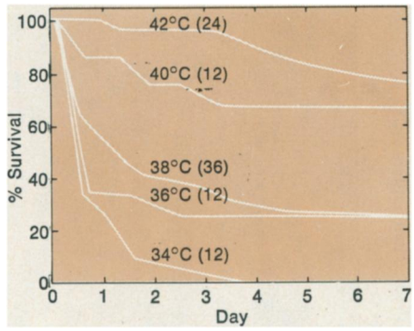

Figure 4. Graph shows percentage survival of desert iguanas (*D. dorsalis*) injected with live *A. hydrophila* and maintained at temperatures ranging from 34°C to 42°C. The total number of lizards in each group is given in parentheses. (From Kluger et al. 1975.)

The role of iron in infection has also recently received considerable attention. It is known that serum iron levels fall during infections (see Weinberg 1974). Garibaldi has suggested (1972) that a fever might be beneficial because at elevated temperatures the pathogenic bacteria cannot obtain or chelate sufficient iron for their normal growth. Using the lizard *D. dorsalis* we investigated this possibility (Grieger and Kluger 1977). Injection of lizards with *A. hydrophila* led to a decline in serum iron levels similar to that found in mammals. This decline was independent of body temperature. In vitro, *A. hydrophila* grew equally well at 38°C and at 41°C; but when iron levels of the medium were reduced, the inhibition of the growth rate was greater at 41°C than at 38°C. This suggests that at febrile temperatures (41°C) iron is required by these pathogenic bacteria in greater amounts than at normal or afebrile temperatures.

To determine whether administration of iron to bacterially infected lizards led to increased mortality, two groups of lizards were infected with live *A. hydrophila;* they were then maintained at a febrile body temperature (41°C) and given either excess iron (5 mg Fe/kg in saline, i.p.) or saline alone. A statistically significant increase in mortality was associated with the administration of excess iron. These results indicate that fever increases the bacteria's need for iron, which in conjunction with a bacterially triggered reduction in serum iron levels may partially account for the adaptive value of fever previously demonstrated in these lizards.

A rise in body temperature will undoubtedly turn out to have profound effects on many other biochemical reactions affecting the host's immunological defense systems. Clearly, more work needs to be done to define precisely which specific aspects of the host's defense mechanisms are enhanced by an elevation in body temperature.

Methodological and clinical implications

The significance of the data presented here can be divided into two general areas. The first concerns the use of the comparative biological approach to basic biomedical problems, which in this case has increased our understanding of the biology of fever. By means of this approach, we have been able to determine that fever apparently has a long phylogenetic history, with vertebrates from fishes through mammals developing fevers in response to bacterial infection. This premise allowed us to look among nonmammalian vertebrates as well as mammals for suitable animal models for our investigation.

Clearly, the desert iguana is an excellent model for our purposes, developing in response to infection a fever that parallels mammalian fever in every characteristic tested. Because of the ease with which the experimenter can manipulate the body temperature of these animals, the desert iguana has been extremely useful both in exploring the role of fever in disease and in identifying possible mechanisms behind the adaptive value of fever. The use of ectothermic vertebrates also allowed us to distinguish more easily between fever and hyperthermia. While the body temperatures of febrile and hyperthermic animals are often similar, the mechanisms responsible for the elevated temperatures are quite different.

Second, and perhaps more important, are the potential clinical implications of these data, which suggest that a fever during bacterial infection is beneficial. If a fever in response to infection does have a general adaptive value in ectotherms, then an inexpensive therapeutic procedure is readily available for diseased ectotherms maintained in captivity: simply provide a source of heat.

If after careful investigation moderate fever is also shown to increase survival rates for birds and mammals, then the use of antipyretic drugs would be contraindicated. Perhaps drugs which are analgesic but not antipyretic, reducing pain rather than the fever itself, could be substituted for the commonly used drugs, which reduce both. It appears that we may be on the verge of verifying Sydenham's hunch that "fever is a mighty engine which Nature brings into the world for the conquest of her enemies" (1666).

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