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Biological Basis of the Behavior of Sick Animals

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HART, B. L. *Biological basis of the behavior of sick animals.* NEUROSCI BIOBEHAV REV 12(2) 123–137, 1988.— The most commonly recognized behavioral patterns of animals and people at the onset of febrile infectious diseases are lethargy, depression, anorexia, and reduction in grooming. Findings from recent lines of research are reviewed to formulate the perspective that the behavior of sick animals and people is not a maladaptive response or the effect of debilitation, but rather an organized, evolved behavioral strategy to facilitate the role of fever in combating viral and bacterial infections. The sick individual is viewed as being at a life or death juncture and its behavior is an all-out effort to overcome the disease.

Fever Interleukin-1 Anorexia Sleep Depression Disease

ALMOST everything that is written about the species-typical behavioral patterns of animals, including discussions of adaptive significance, ultimate causation, proximate causation, and physiological determinants, involves the behavior of healthy animals. The behavior of sick animals is not mentioned in the context of discussion of the function of behavior, presumably on the assumption that the behavior is not particularly adaptive and is the result of debilitation from a disease process along with secondary effects such as inability to obtain food and water. Animals that are acutely ill with systemic protozoan, bacterial or viral infections are typically described as depressed and lethargic with little interest in eating food and drinking water. A little later in the course of a disease they commonly show signs of dehydration along with indications that they have lost interest in grooming since they develop rough hair coats. These behavioral signs generally accompany a fever response and, together with the occurrence of fever, are recognized by animal handlers and veterinarians as signs that an animal is sick or is becoming sick with an infectious disease.

This picture of the lethargic, depressed, anorexic, and febrile individual is not specific to any particular animal species, but is seen in humans and a variety of animals, and the behavioral signs are seen with a variety of systemic diseases as well as with some more localized infections. Some recent research, especially that demonstrating the role of fever in facilitating a person's or an animal's ability to combat viral and bacterial infections, has led to the development of a perspective presented here that the behavior of a sick individual is not a maladaptive and undesirable effect of illness but rather a highly organized behavioral strategy that is at times critical to the survival of an individual if it were living in the wild state. In this paper I will present an overview of the possible adaptive and functional values of the behavior typical of sick animals and people. Some aspects of the perspective have been briefly outlined before [72,73]. Although the emphasis is on animals, the concepts are relevant to human biobehavioral science and could be of use in understanding behavioral aspects of human illness.

Perhaps because our view of infectious disease is so shaped by an orientation on the importance of vaccinations, chemotherapeutic treatment, and supportive therapy, we tend to overlook the fact that animals and people have been exposed to, and have survived, the effects of disease-causing organisms through millions of years of evolutionary history. The coevolution of the host-pathogen or host-parasite relationship is by now well established in evolutionary biology [59,138]. Indeed exceedingly complex nonspecific and specific immunologic systems of mammals [160] provide documentation of the evolved strategy of animals to prevent infections by pathogens or to survive established infections. It is quite logical to expect animals and people to also have evolved nonimmunologic disease-fighting strategies, including behavioral patterns, that might serve as a first line of defense before the nonspecific and specific immunologic systems are activated and that would complement or potentiate immunolgical processes.

When a wild animal is acutely ill with a pathogen it is at a life-or-death juncture. The behavior associated with being sick can be viewed as an all-out effort to overcome the disease, putting virtually all the animal's resources into killing off the invading pathogen. The behavior associated with being sick centers around the fever response. When animals are initially infected with a pathogen the febrile response, coupled with a reduction of plasma levels of iron, has the effect of inhibiting the growth of at least some viral and bacterial pathogens and is associated with activating elements in the immunological system. The concept to be developed here is that because fever is costly from the standpoint of metabolic activity associated with the rise in body temperature, the depression and anorexia typically seen in sick animals constitute a programmed behavioral mode to

facilitate the body's attempt to raise and maintain a febrile temperature and lower blood iron concentration.

The intriguing history of how fever was viewed in previous cultures and civilizations has been reviewed by Kluger [93] and Atkins [3]. The ancient Greeks believed fever was associated with an imbalance of body fluids or humors and was reflected in various diseases. This concept is largely attributed to Aristotle, although Hippocrates certainly recognized and wrote about the occurrence of elevated body temperature in certain human disease states. Fever, as a primary marker of disease, is mentioned in both the Old and New Testaments and was considered as God's Punishment for human transgressions. In the Middle Ages fever was almost synonymous with the Black Death which killed one-fourth to one-third of the European population. It was not until 1953 that it was clearly demonstrated that leukocytes secreted a fever-inducing factor [19], a finding which soon led to the notion that bacteria and viruses cause leukocytes to release the fever-inducing factor. Although elevated body temperature has long been viewed as a symptom of illness in both people and animals, until recently, fever has typically been thought of as an undesirable side effect of illness to be reduced by antipyretics such as aspirin.

The widespread occurrence of a physiological mechanism by which the body's cells produce a factor to cause a regulated elevated body temperature was recognized by Kluger [92,94] as an evolved mechanism going far back in vertebrate evolutionary time and which probably had some adaptive value in combating disease. Evidence initially coming from Kluger's laboratory (discussed below), and accumulating in other laboratories, points to the value of fever in suppressing bacterial and viral growth in the body in a number of instances among vertebrates and in potentiating various aspects of the immune system in mammalian species. A thesis of this paper is that just as animals and people have evolved an emergency thermoregulatory mode to deal with the onset of infectious diseases, they have also evolved an emergency behavioral mode which potentiates the thermoregulatory mode. The behavioral mode, characterized by sleepiness, depression, loss of appetite, reduction of water intake, and cessation of grooming, are as common and ubiquitous among animal species when they are sick as is the occurrence of fever. However, the conceptual building blocks for understanding the physiological regulation of fever, sleep, and appetite have only recently been elucidated to the point that one can argue that the behavior of sick animals and people is not the result of debilitation but an adaptive strategy with survival implications. Understanding the biological basis of the behavior typical of sick animals and people can contribute towards more informed and intelligent medical care of sick people and animals.

This review will discuss first, as essential background, the role of fever in combating viral and bacterial infections. The behavior of sick animals will be dealt with next under the headings of: "Anorexia and Increased Threshold for Thirst," "Sleepiness and Depression," and, "Reduced Grooming and Altered Physical Appearance of the Animal," A heading entitled, "Overview of the Behavior of Sick Animals and People," surveys the common infectious diseases of animals and people to examine how well the concepts presented fit the clinical descriptions of acute infectious diseases. Finally the notion of a prophylactic fever for animals such as lactating mothers, where illness would be catastrophic or where animals are particularly vulnerable to infections, is discussed under the heading of "Prophylactic Fever."

ROLE OF FEVER IN COMBATING ACUTE INFECTIONS

The fever response is initiated by the release of activators, such as the components of the cell walls of bacteria, which induce the synthesis of what have been commonly known as endogenous pyrogens from fixed tissue macrophages, blood monocytes, phagocytic cells of the liver and spleen, and granular lymphocytes. The activated cells release such endogenous pyrogens (EPs) with infections from many types of viruses, bacteria, and protozoa, as well as with some hypersensitivities and tissue necroses. One of the EPs, and perhaps the primary one, is interleukin-1 (IL-1) which as been known before as leukocytic endogenous mediator and lymphocyte-activating factor [47,98]. IL-1 is not only involved in causing fever but also in inducing other fever-related responses such as lowering plasma concentrations of iron (hypoferremia) and zinc (hypozincemia), increasing the excretion of sodium and in activating nonspecific resistance to pathogens [47,50]. IL-1 causes the release of adrenocorticotropic hormone and glucocorticoids [23], which presumably play a role in helping the animal to meet the stress and energy demands associated with illness. The adrenocorticotropic hormone release is mediated through the action of IL-1 in stimulating the secretion of hypothalamic corticotropin-releasing factor [21, 146, 168]. Tumor necrosis factor is another EP and shares many of the biological properties of IL-1 [24, 49, 102]. Another EP is interferon-β_2, recently identified as interleukin-6 and which is released from some of the same cellular elements as IL-1 [1, 115, 132]. Interleukin-6 is identical to what was previously known as hepatocyte stimulating factor and together with IL-1 and tumor necrosis factor, promotes the release of proteins from the liver including C-reactive protein, serum amyloid A, ceruloplasmin, haptoglobin, antiproteinase and fibrinogen [65,136].

The fever response is thus part of a cluster of physiological alterations, induced by the release of EPs as a generalized reaction to microbial or viral infections and is often referred to as the acute-phase response in the host. The proteins produced by the liver are referred to as acute-phase proteins. Aside from the release of acute-phase proteins from the liver, the primary mediator of fever is still thought of as IL-1, and in this paper EP and IL-1 are used interchangeably unless otherwise indicated. New information is accumulating rapidly regarding details and differences in the biological action of various EPs. This review is oriented so as to be presumably applicable to the behavior of sick animals regardless of details of cellular mechanisms by which EPs activate the acute-phase response.

The febrile response is due to EPs changing the hypothalamic thermoregulatory set point or thermostatic setting. The thermostatic setting is raised so that an animal feels cold at previous normal temperatures. A new thermal equilibrium is reached as the animal conserves body heat by shunting blood from peripheral tissues to internal organs, producing piloerection, and if necessary increasing metabolism by shivering to produce heat. Behaviorally one sees animals seeking warm environments and attempting to reduce exposed body surface area by curling up.

A possible mechanism by which EPs stimulate the hypothalamus to raise the set point is to promote increased synthesis of prostaglandins [120]. Drugs that are used to reduce fever such as salicylic acid are known to block prostaglandin synthesis. Central nervous system regulation of some of the acute-phase response such as fever induction, depression of appetite and increased sleep (see later) may be modulated by

neural elements in the brain which contain IL-1 [28]. Some evidence also suggests that EPs express their influences on the hypothalamus through cyclic AMP, norepinephrine, sodium-calcium ratios or other mediators [38,122]. Arginine vasopressin has been found to be released during fever and hyperthermia and acts as an antipyretic counter to EPs [144,181].

Value of Fever in Infectious Diseases

One of the earliest experimental reports of the importance of body temperature in the control of infections was by Muschenheim *et al.* [129] who studied dermal pneumococcus infections in rabbits that were subjected to environmentally induced hypothermia. Infection with a strain of pneumococcus that was nonlethal under ordinary conditions produced an overwhelming bacteremia and death in hypothermic rabbits.

The first evidence of the value of febrile body temperature in fighting disease has come from experiments by Kluger and his associates, taking advantage of the fact that one can regulate body temperature of cold-blooded reptiles by environmental means. For example, there were pronounced differences in survival rates of lizards (*Dipsosaurus dorsalis*) subjected to a bacterial infection (*Aeromonas hydrophilia*) when they were kept in cold versus warm environments [95]. When lizards were kept in the same environment where a fever occurred sufficient to allow survival of almost all animals, treating animals with an antipyretic resulted in death in lizards in which the fever was prevented [22]. In a different laboratory it was found that survival of fish infected with a pathogen was also enhanced if the animals were allowed to develop fever [42].

Later experiments involved warm-blooded animals. In an experiment from Kluger's laboratory [97] a drug was used to suppress fever in rabbits infected with *Pasteurella multocida*, a pathogen that causes a lung disease. Investigators found that rabbits were much more likely to die when given an antipyretic than the control subjects allowed to develop fever. Ferrets can be infected with the human influenza virus which produces a disease similar to that in people. In one study a reduction in virus titers in nasal washings were correlated with increases in temperature from a febrile reaction [165]. In a follow-up study a causal relation between the temperature increase and suppression of viral replication was demonstrated when ferrets were found to shed fewer viruses in the nasal discharges if they were allowed to have a fever than if the fever was blocked by shaving them or treating them with an antipyretic [80].

It should not be assumed a higher temperature is always better in terms of host resistance to a pathogen. In one experiment rats, which were infected with *Salmonella enteritidis* and induced to develop an artificially high fever through hypothalamic cooling, had a higher mortality rate than controls [7]. Perhaps, as conjectured by the investigator, a moderate fever would have beneficial effects but a higher fever was detrimental because of metabolic or endocrine responses induced by the high temperature.

The value of fever in treating infectious diseases of people caused by pathogenic organisms with low thermal death points has been known for some time. The spirochete causing syphilis is one such microorganism. Wagner-Jauregg discovered that neurosyphilis could be successfully treated by giving patients malaria which produced a very high fever. The malarial organism strain used was rather easily treated with quinine once the series of artificial fever episodes was conducted. Treating neurosyphilis, especially the paretic form, with malaria therapy introduced the therapeutic technique of fever therapy and Wagner-Juaregg was eventually awarded the Nobel Prize for this development [118]. Malaria therapy remained a standard treatment option for the paretic form of neurosyphilis through World War II. Fever therapy found greater utilization in the treatment of gonorrhea which is caused by another organism with a low thermal death point. This form of treatment for gonorrhea remained the only successful treatment until the advent of penicillin [106].

Another perspective on the role of fever in survival from infectious disease comes from work on elderly patients. Recent studies have documented the clinical impressions of physicians that elderly patients at an advanced age often have no fever or a blunted febrile response to infection [133]. In one study of patients of a mean age of 81 there was minimal to no fever in the presence of bacteremia [68]. In another study elderly patients with *Streptococcus pneumonae* bacteremia had lower mean and lower peak febrile responses than a group of younger patients with the same infections [62].

The blunted fever response would appear to be related to a generally recognized pattern of more severe illness and higher mortality of elderly patients with infectious diseases [174]. In comprehensive studies of bacteremia or fungemia in adult human patients, it was found that patients that had lower or no febrile responses had a high mortality [29,176]. Consistent with other studies cited, the patients with lower or no fever reaction to bacteremia were older.

An animal study along the same lines is one comparing young and old mice which were injected with *Salmonella typhosa* endotoxin. It was found that the older mice could not achieve a fever at an environmental temperature below the thermoneutral zone and suffered a higher mortality than younger mice which did exhibit fever under the same conditions [76].

Mechanisms by Which Fever Combats Infections

Analysis of the fever response in warm-blooded animals reveals that the increase in body temperature can be quite easily triggered and observed within a few hours after infection with a pathogenic organism [47]. There seem to be two primary mechanisms by which a fever facilitates an animal's ability to deal with infectious disease. One of these is by the influence of temperature elevation in potentiating immunological responses. Fever may potentiate nonspecific immune reactions by increasing bacterial killing by neutrophils [149] and specific immune responses by accelerating and enhancing lymphocyte proliferative responses to antigens or mitogens [53, 113, 153] and enhancing antibody synthesis [9,83]. Although these effects are partially attributed to the elevation of body temperature, IL-1 itself activates lymphocytes (important for initiation of cellular and humoral immune mechanisms) and induces the synthesis of molecules that in turn activate lymphocytes [48,50]. Febrile temperatures have been found to potentiate the IL-1 induction of T-cell proliferation [52]. As mentioned above, the increased hepatic synthesis of acute-phase plasma proteins which serve nonspecific host defense functions [48], is believed to be due to stimulation by IL-6 along with IL-1 and tumor necrosis factor [65,136].

The second mechanism by which fever benefits acute ill animals relates to the fact that some pathogens have an optimal temperature for growth that is the same as or below the normal body temperature of the animals they infect. There is

now evidence that both in vitro and in vivo studies that there is a direct suppressive effect of temperature elevation on the growth of some pathogenic viruses and bacteria. In experimental pneumococcal meningitis in rabbits, blocking the febrile response lowered the doubling time of the pathogen in cerebrospinal fluid to less than one half. In vitro growth of the pneumococci, which grew well at 37°C, was nonexistent at the typical febrile temperature of 41°C [152]. In a study typical of those done with viruses it was found that canine herpes virus replicates in dog kidney cell culture much slower at temperatures elevated above body temperature [31]. The primary human pathogens for which typical febrile temperatures have proven inhibitory of in vitro growth are pneumococci and those causing syphilis and gonorrhea [110].

Not all pathogenic organisms for which fever provides some protection to the host are suppressed in vitro by febrile temperatures. For example, while survival from pasteurellosis in rabbits is decreased by intrahypothalamic infusions of small quantities of the antipyretic salicylic acid which blocks the fever reaction [170], in vitro growth of the pathogen, *Pasteurella multocida* is not suppressed at the febrile temperature of 42°C compared with the normal 39°C rabbit temperature [97].

Reduction of Plasma Iron Concentration

One of the physiological changes that accompany the fever response is a reduction in plasma iron and zinc concentrations. This is true of most infections accompanied by fever in people and laboratory animals [175]. Among domestic animals a fall in plasma iron and zinc is reported for cattle infected with rhinotracheitis virus or *E. coli* endotoxin [46] and in cattle with mastitis [172]. Iron is an essential element for many bacteria and they obtain iron needed for their own multiplication by chelating the small amount of free iron in the blood that is bound to serum transferrin [30, 57, 175]. Transferrin is a glycoprotein which plays a role in the transport of iron among its sites of absorption, storage and utilization. The reduction of iron is due to redistribution of iron in the body rather than excretion [90]. This sequestration is brought about by a greatly reduced release of heme-derived iron from the reticuloendothelial system back into the serum transferrin iron pool. There is virtual absence of the return to plasma of iron from erythrocytes which are broken down by the reticuloendothelial system [105]. The importance of iron for bacterial growth and the mechanisms by which iron binding proteins of the body normally maintain low concentrations of free iron as an element of resistance to infection has been reviewed [25, 30, 175].

Laboratory experiments have now shown that the increase in body temperature, if accompanied by a reduction in plasma iron, is particularly inhibitive to the growth of some bacteria that are grown in vitro. The synergetic effect of febrile temperatures and plasma iron reduction has been shown in some in vitro experiments that use iron levels in culture media representing that normally found in plasma to contrast with a level in culture media representing the low iron concentration found during a febrile response. With *P. multocida*, which causes the common disease of pasteurellosis in rabbits, the growth of the pathogen is not inhibited at normal temperatures (39°C) with either normal or low iron concentration in the media nor is it inhibited at moderate febrile temperatures (41°C) with normal iron levels. However, with low iron levels a moderate fever is inhibitive just as is a high fever (43°C) with normal iron levels [96]. Essentially the same picture of synergism between moderate febrile temperatures and low iron levels was seen with *A. hydrophila*, the previously mentioned pathogen of lizards [69]. Also work with lizards revealed that when the animals were given excessive iron while infected with the pathogen and allowed to have a fever response, the death rate increased compared with animals given no supplementary iron [69]. Meningitis in mice, caused by *Neisseria meningitidis*, has been found to progress and disappear in concert with the disappearance of iron from the transferrin pool [78]. Administration of iron dextran to mice enhances the infection caused by *N. Meningitidis* [78], and administration of iron bound to transferrin resulted in 100 percent mortality in mice compared with no mortality in control mice [79]. In vitro growth of *N. meningitidis* is limited by iron availability, and the growth limitation is relieved by the addition of iron bound to transferrin [79].

For some pathogens which cause disease and for which fever is not characteristic, the reduction of available iron coupled with elevated temperatures can have inhibitory influences. Growth of the yeast, *Candida albicans*, which causes some localized disease conditions in people, is suppressed in vitro when grown at normal human febrile conditions and the medium is depleted of iron and zinc [81]. Circumstantial evidence of the influence of iron reduction in combatting infectious disease was found in a study of Somali nomads that are typically iron deficient for dietary reasons. Somali patients which were treated with iron supplement had 4 times as many episodes of infectious diseases, including brucellosis, tuberculosis, pneumonia and malaria, as patients receiving a placebo [128].

In patients undergoing elective surgery, such as cholecystectomy, there is a marked drop in serum iron concentration. It has been hypothesized that this represents a physiological mechanism to protect the host from infection associated with open wounds [6]. The fever that is often seen postoperatively, or after trauma, would act synergistically with iron reduction to inhibit bacterial contamination.

Several experiments have revealed that it is the release of IL-1, not the elevated temperature, that is responsible for lowering of iron and zinc concentration [48, 50, 175]. Typical of animal experiments is one in goats where injection of *E. coli* endotoxin results in fever, shivering, hypoferremia, hypozincemia. In these goats blocking the fever with the antipyrogen, flurbiprofen, did not prevent the decrease in plasma iron or zinc concentration [169] presumably because the antipyrogen acts at the level of the hypothalamus rather than on the release of IL-1. The lowering of plasma zinc concentrations, which is regularly seen with infections [15], may be important in combatting some infectious diseases and not others [164].

Fever as an Evolved Strategy

The relationship between fever and enhanced survival in animals is not uniformly a consistent one. As Blatteis [26] points out, the use of antipyretics in treatment of infectious diseases of people has been a common practice for a long time. If the use of antipyretics led to markedly increased morbidity and mortality this undoubtedly would have been noted clinically long ago. I have cited some studies revealing a correlation between fever and survival in human patients with infectious disease. In other instances, however, no correlation [56], or even negative correlation, can be found [20]. Certainly not all infections or infectious diseases result in

fever [4], and there are wide individual variations in febrile responses to the same pathogens. In animals, this variability has been documented in rabbits [155]. With the current high level of medical treatment of both humans and domestic animals, the occurrence of fever is not always an essential mode of host resistance.

The purpose of this paper is to argue that the fever response and accompanying behavioral changes characterized by anorexia, depression, increased threshold to thirst, and cessation of grooming, evolved as adaptive strategies in animals and humans as a way of fighting infectious diseases when medical care was nonexistent. As a strategy, it would not necessarily fit all infections and certainly not be successful all of the time, or even most of the time. For an evolved strategy to be selected for, it needs to have proved beneficial in saving individual lives some of the time. In animals and people prolonged temperatures above 41°C can be associated with tissue damage such as degeneration of neuronal, hepatic and cardiac tissue. Yet febrile temperatures occasionally lie within this range for infectious diseases. Ewald [59] has pointed out that to the wild animal such a fever response could still be adaptive if on average the overall benefit from the high fever was greater than the net cost of some tissue damage due to the higher febrile temperature. The frequency of success of the fever-related strategy is also related to the degree to which pathogens have evolved resistance to host protective mechanisms [135], including resistance to the effects of febrile temperatures.

The occurrence of a fever response at the outset of infection by a pathogen is ubiquitous among vertebrates, having been documented in fish, amphibians, reptiles, birds and mammals. For such a physiological response to be so persistent throughout vertebrate evolution strongly suggests an adaptive function in enhancing an animal's ability to combat infectious disease [92,93]. An equally compelling argument can be made that the production of fever is metabolically very costly to an animal and thus for the physiological response of fever to have persisted in evolution, there must be some potential benefits to survival [92,93]. The energetic costs of fever are discussed below as the last topic of this section.

Energetic Costs of Fever

Once the thermoregulatory set point is elevated, raising and maintaining body temperature to reach the demand of this new set point can be met by reducing heat loss and, if necessary, increasing heat production through increased metabolism. Heat loss reduction can be achieved behaviorally by means such as curling up, huddling, seeking warm places and, physiologically, by shifting blood flow from the skin to the interior parts of the body. Piloerection, to increase insulating properties of the fur coat, is also helpful in reducing heat loss. Heat production is gained through muscle contraction (shivering and nonshivering), nonmuscular metabolic activities and brown fat metabolism in some smaller mammals [74].

The initial work in estimating the amount of heat production involved in maintaining a fever in humans was undertaken on human patients suffering from malaria, typhoid, tuberculosis or erysipelas, or injected with a forein protein [11]. Calculations were made after patients had experienced a chill, shivering had subsided, and the patient had achieved a stable elevated temperature. The various fever reactions caused an increase in metabolism of 30–50 percent. Malaria produced increases in metabolism to near 50 percent. The overall mean percent increase in metabolism per 1°C of fever was estimated at 13 percent. The work was summarized by Dubois [54,55] and more recent reviews of thermoregulation still accept this 13 percent figure for the cost of fevers [74,93].

The increased energetic costs are partially a function of the direct effect of increased temperature in accelerating metabolic processes (the so-called Q_{10} effect) [74], and partially a function of an increase in metabolism (shivering) necessary to raise body temperature. The extent to which an increase in metabolism is needed to produce each 1°C fever among various species of animals is difficult to say. Obviously, with differences in body size giving different surface-to-body-mass ratios, differences in hair coat density, hair or skin color, and differences in habitat (e.g., temperate climates versus arctic areas) the energetic cost of fever production will differ among various species of mammals. The more efficient are the heat conservation mechanisms the less energy will be spent on maintaining fever by metabolic means. When body temperature is raised by shivering, which is the most important involuntary mechanism of thermoregulatory heat production in adult people and larger mammals, the metabolic rate is increased 2–3 times that of resting level in man and up to 5 times that in dogs [74]. Involuntary muscle activity can be observable as in shivering, or invisible and only detectable by electromyography.

A consequence of a prolonged acute-phase response is muscle proteolysis and negative nitrogen balance [10,14]. The muscle proteolysis, which is enhanced by elevated body temperature, is utilized in gluconeogenesis to help fuel the energy requirements for fever and for the release of amino acids which are utilized for proliferation of lymphocytes, production of immunoglobins, and synthesis of collagen for tissue repair [48,174].

It is the high metabolic cost of the fever response, and the threat of higher costs if shivering must be activated to increase or maintain a fever, plus the advantage of lowering plasma concentration of free iron, that can explain the function and adaptiveness of behavior typically associated with sick animals.

ANOREXIA AND INCREASED THRESHOLD FOR THIRST

On the surface, the occurrence of anorexia seems somewhat paradoxical. Febrile animals not only need calories to fuel the needs of an elevated body temperature and to reduce the demand for muscle proteolysis, but they also need replacement protein for tissue breakdown due to direct effects of the disease causing organism. Looking at the situation of the animal in the wild, one can see that by not consuming food it reduces the chance of raising plasma concentrations of free iron from foodstuffs containing iron. The animal's body is sequestering away iron and the influx of new iron into the bloodstream would, therefore, be counterproductive. This is a greater risk in carnivores that can take in more iron in a short period of time than in foraging herbivores.

Both anorexia and a possible reduction in drinking water relate to the notion that an animal that does not feel hungry or thirsty has little motivation to move about in search of food and water. If an animal stays in one spot, it engages in much less muscular activity and thus can save on body energy reserves needed for the increased metabolic costs of fever. Perhaps more important, by staying in one place it is able to reduce heat loss which would otherwise occur from

increased convection and enhanced body surface exposure if the animal was moving about. In addition, for some animals that are subject to predation, reduced motivation to seek food and water reduces the likelihood of predation compared with moving and with impaired locomotor ability.

Experimental studies on fever-related anorexia reveal that IL-1 rather than hyperthermia per se induces anorexia since administering an antipyretic, along with endotoxin to stimulate IL-1 release, still resulted in reduced food intake. Furthermore, injection of IL-1 resulted in suppression of food intake in fasted rats [108]. Since application of IL-1 to the brain areas near the hypothalamic satiety center does not suppress food intake, it appears as though IL-1 acts peripherally, perhaps in the liver to bring about anorexia [109]. The food intake suppression seen in fasted laboratory rats injected with endotoxin of IL-1 is not absolute, but is rather about 60–70% of ad lib normal intake [107]. In another study continuous administration of recombinant IL-1 for 4 days to rats reduced body weight and eating behavior by about one half. The rats were kept on a 12–12 light dark cycle and eating behavior during the active (dark) period was reduced in IL-1 infused rats to the equivalent of the eating behavior of control rats during the inactive (light) period [134]. During days 4 and 5 of continuous infusion eating behavior began to increase towards control levels, suggesting a possible self limiting aspect to anorexia.

It is not uncommon to see a willingness to take some food during an infectious illness in both people and domestic animals where food is provided with easy access. In the wild situation, however, it may take considerable effort on the part of animals to forage or hunt for food and the reduced motivation to eat, as represented by a reduction of 60–70% of normal appetite, may translate into a more pronounced suppression of food intake.

The old adage "feed a cold and starve a fever" may have some biological basis as a reflection of the relationship between fever and anorexia. Since the common cold usually does not result in fever, one would suspect little IL-1 has been released, hence little suppression of appetite would be expected. In a febrile disease like influenza where IL-1 is released, a loss of appetite and cessation of eating is common.

The effect of the fever response on the drinking behavior of animals is not clear at this point. Sick animals are commonly dehydrated which may reflect decreased access to water, the effects of intestinal water loss if an animal has diarrhea and possibly an increased threshold of thirst. A way of documenting an increase in thirst threshold in animals is by determining the level of plasma osmolality at which an animal initiates drinking. In one experiment it was found that heating the preoptic area by 0.5–2.4°C, as would happen with an increase in core body temperature, suppressed osmotic thirst in dogs [156]. In subsequent studies a pyrogen (lipopolysaccharide fraction of *E. coli*) was administered to dogs. After the elevated temperature had stabilized (about two hours after pyrogen administration) the increment in plasma osmolality needed to elicit drinking was found to be much higher than in control dogs [157]. A contrasting picture comes from the study involving continuous administration of IL-1 to rats [134]. Although these animals showed no change in drinking during the active phase there was an increase in drinking during the the inactive phase. Further studies would be needed to reveal if the increase in drinking during the inactive phase in the laboratory would be indicative of increased thirst in rats in the wild, who are in a burrow during the inactive period.

One way that a reduction in the need to drink water may come about is with reduced plasma osmolality through increased sodium excretion. Correspondingly, recent studies show that IL-1 administration to rats decreases sodium reabsorption by the kidneys [12,35]. Thus the body may be attenuating the hypertonicity from reduced water intake by increased sodium excretion as a way of complementing a possible increased threshold to osmotic thirst.

There is a precedent for proposing a type of programmed reduction of interest in eating or drinking as an adaptive mechanism, and this is with mammals that hibernate and in some birds that incubate eggs. For hibernating mammals, foraging for food or consuming water during occasional winter arousals would be counterproductive because the kidneys do not function well when hypothermic and to eliminate metabolic end products the kidney would have to warm up which is contrary to the winter survival strategy [123]. During egg incubation in a number of species of birds which do not share incubation with a partner, to leave the nest and feed or drink would endanger the viability of the eggs. Thus, it is argued that hibernating animals and birds incubating eggs do not get hungrier and hungrier even though they may have lost considerable weight. Rather, they do not feel hungry because they have a lowered regulatory set point for body caloric needs that is programmed for these particular functions [123,124].

Finally, in supporting the argument that a programmed anorexia is part of the fever response, there are some experimental studies illustrating the value of anorexia in combating diseases. Experiments on mice have shown that force feeding during bacterial infections can reduce survival time and increase mortality [127]. If food deprivation is employed two to three days before the bacterial infection (listeriosis) in mice, however, survival rates can be increased [179].

SLEEPINESS AND DEPRESSION

Sick animals are frequently described as depressed, meaning that they are inactive, lethargic, sleepy or uninterested in surroundings. People who are afflicted with systemic illnesses such as influenza commonly described themselves as feeling depressed, tired, sleepy, or weak. Certainly the particular terms used to describe the demeanor of a sick animal are somewhat arbitrary, depending upon the background of the person making the description, and how the observer would expect to feel as a sick animal. Although the term depression is used, a common element underlying all the descriptions of both sick animals and sick people is that of increased sleepiness or a tendency to sleep during normal periods of wakefulness.

In correspondence with the clinical observations on animals and subjective reports in people of increased sleepiness during many illnesses, there is experimental work pointing to the fact that IL-1 induces excessive sleep in animals and humans. In both rabbits [101] and rats [163] cerebral intraventricular administration of IL-1 causes prolonged slow-wave sleep. Further work on rabbits illustrates that the increased slow-wave sleep is selective and that the duration and number of sleep cycles, or changes in brain temperature that normally occur during transitions from one arousal state to another, remain unchanged during IL-1 infusion [173].

A study of the effects of *Staphylococcus aureus* infection in rabbits revealed enhancement of slow-wave sleep 6–16 hours after injection of the pathogen. The rabbits were febrile 6–48 hours after injection revealing some temporal dissociation of sleep-inducing aspects of the infection from the

febrile-inducing aspects [166]. Other experimental work indicates that endotoxins and the lipid A moiety of the lipopolysaccharide component of bacterial cell walls can also induce excessive slow-wave sleep [100]. Since endotoxin and lipid A stimulate IL-1 release [47], some of the enhancement of slow-wave sleep is undoubtedly through this mechanism. There is evidence, however, of lipid A- and endotoxin-induced increases in slow-wave sleep and decreases in rapid eye movement sleep aside from IL-1 influences [99]. The variability of sleep patterns and febrile responses with different infectious diseases could thus reflect the fact that to some degree activation of the fever response and changes in sleep patterns are modulated by somewhat different, but overlapping, factors.

The study of dealing with continuous IL-1 infusion in rats over 5 days revealed that IL-1 markedly reduced general locomotor and rearing activity during the active phase to levels seen in controls during the inactive phase [134]. This marked reduction of activity could reflect the effects of enhanced sleep and possibly some additional influence of IL-1 on general activity apart from increased sleepiness.

According to the perspective presented here, the sleepy or depressed or inactive animal is less motivated to move about using energy that could fuel metabolic increases associated with fever. In addition, the animal will also curl up or otherwise insulate itself for conservation of body heat, making shivering less necessary. Thus, excessive sleepiness is complementary to anorexia in inducing the animal or person to remain in a heat conservation mode. Investigators working on the sleep promoting aspects of IL-1, and that have linked the subjective feelings of sleepiness in people with infectious diseases to IL-1 release, have emphasized that sleep plays an important role in recuperative processes induced following a disease [100,173]. Although enhancement of sleep is undoubtedly important in recovery from the effect of an infectious disease, the signs of sleepiness in acute sick animals are particularly evident early in the onset of a disease before tissue damage is brought about by the pathogen or before body energy resources are depleted. An example from swine influenza, which is characterized by fever, anorexia and depression serves to illustrate the point. In the words of one clinician: "The onset was sudden, and all or a large part of the herd quickly developed the gravest symptoms. The herd was so sick it could be walked among and even kicked without forcing them to move" [41]. Supporting these clinical observations, the experimental studies with injection of IL-1 [173] or endotoxin [99] reveal an onset of excessive slow-wave within 1 hour which is when the rise in body temperature is evident.

Relevant to the discussion of increased sleepiness, decreased activity and depression is the fact that there are some animal models of depression serving as a precedent for the notion that depression may occur as an adaptive syndrome for last ditch survival which is put into play before an animal's resources are exhausted. For example, work on separation of infants from their mothers [71, 89, 121], or on animals facing a problem of survival with no apparent solution [161], reveals that the depressed state may be viewed as adaptive behavior. According to these models, an animal's chances for survival are better in a depression-conservation-withdrawal mode than in an active fight-flight-energy-expenditure mode. Depression such as that following infant separation from mothers is usually accompanied by a decrease in temperature and in metabolic activity [139], and therefore this specific depression model is not directly applicable to the depression seen in sick animals. The depression referred to in the animal models is viewed as reflecting a physiological mechanism that comes into play when it is adaptive for an animal to go into an energy conservation mode while energy reserves are still ample rather than when the reserves are exhausted.

REDUCED GROOMING AND ALTERED PHYSICAL APPEARANCE

Sick animals often assume a posture that we associate with being sick. For those animals that can easily curl up, such as carnivores, we can see the adaptive value in reducing surface area of the body exposed to the environment for heat loss by convection and radiation. The curled up posture, particularly with accompanying piloerection, is a common sight in sick animals. In large herbivores, the posture is often that of being humped over or even lying down accompanied by piloerection. Given the rather limited flexibility of large herbivores, this is probably the best they can do to conserve body heat. The curled position of the smaller rodents and carnivores is more important than in larger animals since the ratio of body surface area to body mass is proportionally greater in small mammals.

Animals which have been sick for several days or longer often have a scruffy-looking hair coat, apart from piloerection. The scruffiness noted in many species including rodents, felids and ungulates is undoubtedly due to a marked reduction in grooming. Studies and observations on grooming reveal that grooming has several functions including cleaning the fur of dirt and oils which improves its insulating efficiency [162]. A pelage that is dirty and oily is an indication of lack of grooming.

Increased sleep and reduced activity in sick animals may account for the reduction in grooming, but there are additional reasons an animal would possibly forego grooming under the demands of a fever reaction, while letting the insulating benefit of conditioning the pelage slip. For one thing the body movement involved in grooming would result in greater heat loss from more exposure of skin surface and increased air movement over the skin. Secondly, grooming requires utilization of energy for the muscular activity involved. These reasons for reduction of grooming would apply to both oral grooming and hind leg scratching. For oral grooming there is also a loss of water through saliva used in grooming. In rodents oral grooming typically includes a sequence of grooming patterns starting with licking the paws and forelegs, interspersed with face washing, continuing onto other parts of the body and ending with genital grooming [140,145]. With such extensive licking from head to tail it is not surprising that where calculations have been done in rats, it has been determined that one-third of nonevaporative water loss is through grooming [141]. This is comparable to the amount of water lost through urine. For rats, which spend 30–50% of waking time grooming, it has been noted that when deprived of water for 24 hours, they show a 50% decrease in oral grooming [27]. Thus, for a febrile animal that has restricted access to water and is experiencing an increased threshold to thirst as an adaptive mechanism, to reduce oral grooming will conserve water. It has not been determined whether the reduction of grooming in febrile or sick animals is a result of the effects of IL-1 or other EPs, hyperthermia, or the sleepiness and inactivity that accompanies illness.

A dirty hair coat may not be the only cost or sign of reduction in grooming. Species as diverse as rodents and ungulates that are experimentally prevented from oral grooming show an increase in ectoparasites. Mice fitted with col-

TABLE 1

INFECTIOUS DISEASES OF DOMESTIC ANIMALS AND MAN CHARACTERIZED BY FEVER, ANOREXIA, AND DEPRESSION

Common Disease Name	Type of Pathogen	Organ System
Dogs		
Distemper	virus	general
Infectious hepatitis	virus	general
Tracheobronchitis	virus	respiratory
Cats		
Panleukopenia	virus	general
Infectious peritonitis	virus	general
Rhinotracheitis	virus	respiratory
Calcivirus infection	virus	respiratory
Infectious anemia	rickettsia	blood
Cytauxzoonosis	protozoa	blood
Horses		
Influenza	virus	respiratory
Viral arteritis	virus	general
Infectious anemia	virus	blood
Eastern encephalomyelitis	virus	central nervous system
Strangles	bacteria	respiratory
Ehrlichiosis	rickettsia	blood
Swine		
Influenza	virus	respiratory
Cholera	virus	general
African swine fever	virus	general
Pox	virus	general
Rotavirus	virus	gastro-intestinal
Pleuropneumonia	bacteria	respiratory
Erysipelas	bacteria	general
Polyserositis and arthritis	bacteria	general
Cattle		
Rhinotracheitis	virus	respiratory
Virus diarrhea and mucosal disease	virus	gastro-intestinal
Malignant catarrhal fever	virus	respiratory
Shipping fever	bacteria	respiratory
Bacillary hemoglobinuria	bacteria	general
East coast fever	protozoa	blood
Sheep		
Sheep pox	virus	integumentary
Hemorrhagic enterotoxemia	bacteria	gastro-intestinal
Multiple Animal Species		
Foot and mouth disease (ungulates)	virus	general
Rinderpest (ungulates)	virus	general
Rift Valley Fever (ruminants)	virus	general
Blue tongue (ruminants)	virus	general
Malignant edema (ruminants)	bacteria	musculo-skeletal
Salmonellosis (most species)	bacteria	gastro-intestinal
Pasteurellosis (ruminants, swine)	bacteria	respiratory
Anthrax (most species)	bacteria	general
Blackleg (ruminants)	bacteria	musculo-skeletal
Listeriosis (ruminants)	bacteria	central nervous system
Leptospirosis (most species)	spirochete	general
Heart water disease (ruminants)	rickettsia	general
Babesiosis (most species)	protozoa	blood
Anaplasmosis (ruminants)	rickettsia	blood
Trypanosomiasis (ungulates)	protozoa	blood
Human		
Yellow fever	virus	blood
Colorado tick fever	virus	blood
Typhus	rickettsia	general
Rocky Mountain spotted fever	rickettsia	blood
Tuberculosis	bacteria	respiratory
Coccidiomycosis	fungus	respiratory
Infectious mononucleosis	virus	general
Infectious hepatitis	virus	general
Coxsackie virus	virus	respiratory
Chicken pox	virus	general
Influenza	virus	respiratory
Virus pneumonia	virus	respiratory
Mumps	virus	general
Measles	virus	general
Poliomyelitis	virus	general
Cat scratch disease	virus	general
Leptospirosis	spirochete	general
Whooping cough	bacteria	respiratory

lars preventing oral grooming are found to have many more lice than mice able to groom normally [125]. Also, prevention of hind leg scratching in mice results in an increase in lice [16] and mites [177]. Cattle that are restrained from oral grooming by a harness, and that are monitored for numbers of ticks that engorge by feeding on them, have about three times as many engorged ticks as control cattle, when both harnessed and control cattle are exposed to the same number of larval ticks [18,154].

Although not documented extensively, it is a common observation that sick animals often harbor a higher parasite load than healthy animals with presumably the same exposure to ectoparasites [126]. One experimental study related to this question dealt with rats which were being studied for the effects of alcohol ingestion. It was noted that the mice consuming a high level of alcohol had pronounced infestations of lice and mites compared with control rats. The excessive ectoparasite load was attributed to a reduction in grooming [143].

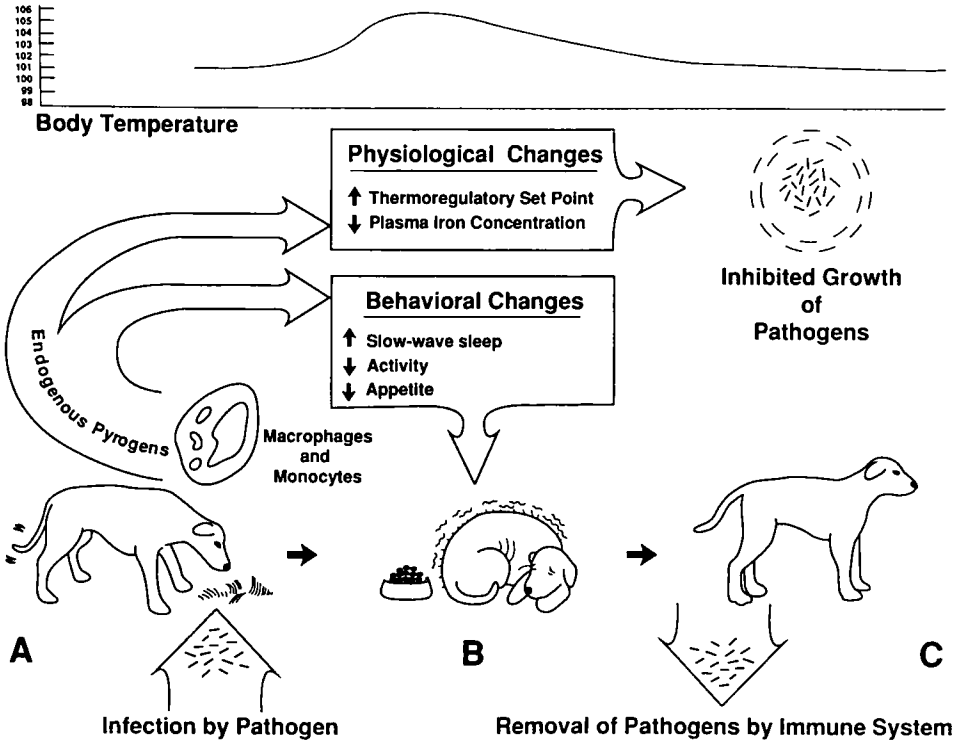

FIG. 1. Illustration of the course of an acute infectious disease from exposure to pathogens (A), through behavioral changes typical of sick animals (B), to recovery (C) with removal of pathogens. The stage portrayed in B may involve dehydration from increased thirst threshold as well as a scruffy hair coat with excessive ectoparasites from reduction of grooming. The behavior typical of sick animals can be viewed as potentiating the fever response reflected in an increase in body temperature.

For animals which carry an increased parasite load for a long time, there is a cost. Evidently the immediate gains in energy and heat conservation by cessation of grooming exceed the costs of a delayed but increasing parasite load. Eventually, during the recuperation phase, if the animal survives, the parasite load can be reduced by renewed grooming activity.

OVERVIEW OF BEHAVIOR OF SICK ANIMALS AND PEOPLE

The picture presented thus far is that the occurrence of fever, anorexia and depression are linked together in being caused, at least partially, by the release of IL-1, and that this link has an adaptive function as an evolved disease-fighting strategy. If this is true then, as a test of this hypothesis, one should find that most infectious diseases of domestic animals and humans, for which fever is characteristic, should be accompanied by anorexia and depression. To address this issue, commonly recognizable infectious diseases characterized by fever, were surveyed in standard textbooks of medicine and infectious diseases for the following species: dogs [34, 37, 45, 58]; cats [33, 36, 45, 58, 88, 178]; horses [87, 112, 131, 142]; swine [17, 103, 117, 158]; cattle [66, 70, 117]; sheep [39, 86, 114, 117]; and humans [13, 60, 61, 75, 111]. Table 1 presents a list of the common viral, bacterial, rickettsial and protozoan diseases of domestic animals and people which were stated to be characterized by fever, anorexia and depression (or similar signs) in at least one reference source. The organ system or systems affected are indicated. For domestic animals, some infectious diseases are infective to more than one species and these are listed under multiple animal species.

As revealed in Table 1, the generalized nature of a febrile reaction accompanied by anorexia and depression is seen with a wide variety of disease patterns and types of causative agents. The same behavioral mode occurs with diseases of low mortality such as feline rhinotracheitis, canine tracheobronchitis, swine influenza, bovine pasteurellosis and human influenza as with highly fatal diseases such as feline infectious peritonitis, canine distemper, hog cholera, bovine malignant catarrhal fever or human yellow fever. Certainly many of the signs of illness vary among diseases depending upon whether the pathogen causes nasal discharge, diarrhea, vomiting, or other pathological signs during the infectious process. The febrile reaction and behavioral mode appear to be almost universally utilized during an invasion by an infectious pathogen regardless of the effects produced by the pathogen acting locally on tissue or organ systems and regardless of whether the disease-causing agent is highly fatal or not. If the behavioral strategy and accompanying fever prove effective, the animal then regains interest in eating, drinking, and grooming; the sleepiness and depression dissipate, and we see the onset of a recovery phase. A schematic representation of the fever response from initial onset to recovery is presented in Fig. 1.

In perusing the animal and human medical literature cited

above, I was able to find only one disease entity in which fever was a noteworthy sign but which was typically not characterized by anorexia or depression. This disease was African horse sickness, a highly fatal viral disease of equids usually transmitted by biting midges and sometimes mosquitoes. Writers in standard clinical texts on equine medicine [112,142], reviews [67] and research reports [116] have commented on the horse's appetite noting they often eat eagerly until within a few hours of death. The persistence of appetite despite a fever of 2–3°C was not invariably true and some case reports of African horse sickness characterized by anorexia and depression were mentioned [116].

This apparent exception of African horse sickness to the rule that fever is accompanied by anorexia and depression, brings up the question of where one might find other examples of fever not accompanied by anorexia and depression. A perusal of the literature on zoo and wild animal diseases [43, 64, 91] reveals that at this time it does not appear as though enough is documented about the behavior and disease course of sick wild animals, in either natural or captive situations, to conduct a clinical survey as with domestic animals. This lack of information about sick wild animals is unfortunate because, whereas domestic animals have all been adapted to temperate climates, some wild animals are native to tropical areas where prevention of heat gain, rather than maintenance of body heat, is the physiological task. Since I have argued that anorexia and depression function to facilitate temperature elevation in febrile animals of species adapted to temperature zones, one might expect to see, as in African horse sickness, that sick animals of tropically adapted species do not display these behavioral patterns since heat gain is easily obtained.

Wild animals that are sick are threatened by increased susceptibility to predation, loss of social position, or removal from territorial holdings. As serious as these consequences may be, death by disease can be even a more immediate threat. The fever response accompanied by anorexia and depression puts virtually all of an animal's resources into recovering from the disease. For an animal unfortunate enough to be infected by microorganisms associated with a deadly disease, taking on the pattern of sick behavior is the most extreme and only strategy an animal in the wild has for surviving. However, in a large population of animals infected with a highly lethal disease there are almost always some survivors. This was seen in the famous rinderpest epidemic that devastated wild ungulate populations in East Africa early in the twentieth century. In these instances it is the survivors that end up with the greatest genetic representation in future generations. Thus, even if confronted with the onset of a disease that is usually fatal, an animal has nothing to lose by going into the sick mode and everything to gain, in terms of reproductive payoff, if it is one of the fortunate few to survive.

PROPHYLACTIC FEVER

Are there situations in an animal's life when the benefits in reproductive success or survival for a time-limited period might warrant a fever-like reaction as a preventative measure when the consequences of contracting an infectious disease would be especially risky? If so, certainly one such situation is in lactating mothers where an illness would jeopardize her ability to care for her infant offspring, where an infection might be passed on to the offspring, or where the infants, which cannot thermoregulate, might be especially susceptible to infectious disease and would benefit from a mother's higher temperature. Consistent with this expectation, mother rats are known to have an elevated body temperature through the first 2 weeks of lactation that is about 1°C over normal. This elevated temperature is a reflection of an increased thermoregulatory set point [104]. A number of experiments by Adels and Leon [2] reveal that the chronic elevation of maternal temperature is probably a reflection of a progesterone-induced increase in the thermoregulatory set point accompanied by corticosterone-induced heat production and heat retention mechanisms. Experiments suggest that developing pups stimulate their mothers to release prolactin and adrenocorticotropic hormone which are responsible, respectively, for the increased progesterone and corticosterone increase. The increase in heat production seems to be an effect of a general increase in tissue metabolism and not a by product of milk production and can be maintained by hormonal stimulation even in the absence of lactation. This elevated body temperature is defended by mothers utilizing either exogenous heat sources and/or endogenous means to the extent possible [2,82].

The fever-like phenomenon seen in mother rats has not been reported in other mammals, which may reflect lack of adequate temperature monitoring in postpartum females or absence of such an effect among mammals in general. Assuming that a fever-like reaction occurs among at least rodents, and possibly other species that give birth to altricial young, it is interesting to examine the phenomenon because the fever of lactating females differs from the fever response of animals with infectious diseases where anorexia, increased threshold to thirst, and sleepiness are present. Rat mothers usually have good appetites and are not dehydrated.

There is evidence that progesterone secretion can stimulate IL-1 release [63]. However, since IL-1 rather than hyperthermia has been shown to induce anorexia and slow-wave sleep, it would appear that in lactating mother rats it is progesterone that induces the elevated thermoregulatory set point without an IL-1 intermediate step. Further evidence of this direct role of progesterone is that the firing rate of preoptic neurons involved in thermal regulation is affected by progesterone [130]. The moderately elevated body temperature of mother rats would appear to be a compromise between normal temperature and that of a febrile rat with an infectious disease where body temperature can be 2–3°C above normal.

There may be benefits for the high heat production of mother rats aside from those possibly related to infectious disease prevention in the mother. In fact, investigators of thermal control in mother rats have not mentioned disease prevention as a possible function but rather stress that benefits might be that milk production occurs more efficiently at higher temperatures [2]. Also mentioned is that high maternal temperature may allow dams to maintain pup temperature more efficiently. This latter point merits additional attention because newborn rat pups, like other altricial species, are incapable of thermoregulating beyond a few degrees of ambient temperature and cannot generate a fever response by internal heat production [171]. The mother's body provides the primary source of external heat. However, infant dogs [84] and rabbits [85] can thermoregulate by moving along a thermal gradient and curling up next to a furred artificial or real mother. Infant rabbits, and presumably other mammals, can develop a fever when given a pyrogen if the pups have access to an external heat source. The experiment documenting this showed that rabbit pups, 12–72 hr

old, moved along a thermally graded alleyway and acquired an elevated body temperature after being injected with a pyrogen [147].

Infant mammals are much more susceptible to many diseases than young animals that have acquired maternal antibody protection [40,150]. Survival of infants exposed to infectious diseases can be promoted by an elevated body temperature. For example, the mortality of suckling mice exposed to Coxsackie B virus was markedly lowered by placing the infant mice in an incubator which maintained their body temperatures higher than at room temperature [159]. Another study was conducted on infection of infant puppies by canine herpes virus which is usually fatal in infants but causes only mild upper respiratory inflammation in older puppies. When infected with the virus, the infant puppies maintained at an elevated temperature had a much longer survival time than infants maintained at a lower temperature. Neutralizing antibody was not found in the long-surviving infants, indicating the increased resistance was due to the inhibitory effect of the elevated temperature on virus replication rather than on immune mechanisms [32]. Similar findings were noted in an experiment on mice [148].

Putting these various bits of evidence together one could conclude that infant mammals exposed to an infectious disease can acquire an elevated body temperature by seeking closer contact with their mothers. For those infants that cannot develop an elevated body temperature above that of their mothers, we can see the value of the elevated temperature of the mother who serves as the heat source making it possible for infants to acquire a modest fever.

There are some other possibilities in the way of prophylactic fevers that are emerging. One is that for animals with diurnal activity cycles, their exposure to pathogens may occur during the active periods rather than the inactive periods. A modest prophylactic fever during the active period may have some protective value. Supporting this notion is a study of rats infected with *Salmonella typhimurium*. When infected at midnight, during the active period for this nocturnal species, mortality was much lower than when infected at noon, during times when rats are normally sleeping [167]. The same study showed that body temperature is highest and plasma iron and zinc concentrations lowest during the night and that these changes, characteristic of fever, were probably mediated by IL-1 release during the active period. Periods of stress represented, for example, in the conventional open-field test for rats, are another time when prophylactic fever might prove beneficial. A recent experiment in rats revealed that open field stress was indeed accompanied by fever. The hyperthermia was blocked by salicylate, indicating that the increase in body temperature was indeed a fever mediated by EP rather than a direct effect of increased muscular activity [151].

CONCLUSIONS AND PRACTICAL IMPLICATIONS

When an animal living in the wild is acutely ill with an infectious disease, it is at a life-or-death juncture. Behavior associated with being sick can be viewed as representing an all-out effort to overcome the infectious disease, putting virtually all the animal's resources into fending off the invading pathogens. The behavioral patterns that we commonly see in people or animals that are acutely ill, including complete or partial anorexia, sleepiness, depression, lack of interest in drinking water and reduction of grooming activity, can be viewed as potentiating the fever or acute phase response by conserving energy and reducing dietary intake of iron. The same behavioral patterns might serve to protect a prey animal from predation while it is acutely ill and its own physical strength compromised. The fever reaction potentiates the animal's immunological mechanisms and there is evidence in some instances that growth of pathogenic bacteria and viruses is substantially reduced by an elevated body temperature, particularly if the fever response is accompanied by a reduction in plasma iron concentration. The behavioral pattern of a sick animal represents a behavioral mode, primarily linked to occurrence of the fever reaction by the secretion of IL-1. This mode is triggered by a wide variety of pathogens ranging from viruses to bacteria to protozoa, and is remarkably similar among species of domestic animals and man.

Although the fever response and accompanying behavioral changes tend to be similar among different diseases within a species, there is some variability. A disease may be characterized by a dramatic and acute onset of fever along with sudden and complete anorexia and depression. In other diseases, anorexia and depression may come about much more slowly or are not complete. Some diseases are characterized by bouts of febrile changes interspersed with more normal temperatures. The variability in behavior and febrile patterns may be due to differences in the disease-causing organisms. Endotoxins produced by bacteria, or products from bacterial cell walls, may influence the sleep-inducing areas of the brain aside from the influence of IL-1 on the same brain areas. Thus, different pathogens could produce different sleep or depression patterns.

Other studies have shown that the hormone vasopressin can influence thermoregulatory mechanisms in a direction opposite that of IL-1 and other EPs, and thus disease factors that influence vasopressin secretion may produce different patterns of febrile changes. Many diseases are accompanied by physical signs associated with the disease such as respiratory distress, vomiting, diarrhea or inflammation that also are reflected in the animal's behavior.

Differences among animals of the same species may also account for some differences in their behavior when they are acutely ill. One experiment illustrates that rabbits that were chronically deprived of protein had an attenuated fever response presumably as a diminished release of IL-1 compared to normal rabbits [77]. This suggests that it is the well-fed and healthy animals that have the most appropriate fever response and are capable of undergoing the most appropriately timed anoretic and depressive phases.

One might expect to find some species in which sick animals would not show anorexia and depression. Species that are native to warm tropical areas and have normal adaptations to keep body temperature from becoming excessively elevated, could acquire a fever with relatively little or no energy conservation and perhaps not become sleepy or depressed.

There are some practical implications for the perspective presented here. Medical experts from both the human and animal fields have pointed to the wisdom of allowing a febrile temperature to occur and using antipyretics mainly when the body temperature threatens to become injurious [5, 44, 119]. In fact, the thermoregulatory ups and downs produced by antipyretics may make an animal less comfortable than constant fever. As a practical matter one could help a sick animal to maintain a moderate increase in body temperature through environmental means such as raising room temperature, using blankets, heating pads or extra bedding [72]. The

behavior of anorexia should be seen as a normal consequence of the fever response and sick individuals not force fed unless in poor condition. If force feeding is necessary the supplement should contain no iron, at least in acute bacterial infections. Chemotherapeutic agents are an important aspect of treating sick people and animals but with the threat of increasing numbers of drug resistant strains of bacteria and when dealing with viruses, the use of management practices that complement the innate disease-coping strategies would seem to be advisable [72,73].

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