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Temperature and Host Defense

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INTRODUCTION

Fever is a response of humans and many animal species to infection (100, 155, 207). Despite many years of speculation and reviews of the subject, a beneficial role of fever for the host in such a setting has not been firmly established (7, 22, 108, 109, 197).

The purpose of this paper is to review data that may eventually help to determine whether fever represents a basic defense mechanism that is of benefit to the host. Consideration is given to effects of temperature in infectious diseases and to the effects of temperature on immune function in infectious and neoplastic diseases. Other aspects of hyperthermic therapy of neoplastic disease have been reviewed elsewhere (92, 151). The use of hypothermia during surgical procedures is not reviewed unless data are presented regarding immune function or response to invading organisms. The absolute temperature considered "febrile" may vary among species. Distinctions between fever and hyperthermia have been made, based upon the relationship of the temperature to the thermoregulatory "set point" (112). In vivo, the responses of the patient or animal to the temperature can differ depending upon whether the temperature examined approaches or exceeds the thermoregulatory set point. Throughout this discussion, however, the terms fever and hyperthermia are used interchangeably and indicate an elevation of temperature above the preferred or normal range of the species.

The mediators of fever appear to be endogenous pyrogens, small proteins synthesized and secreted in response to stimuli by cells usually referred to as "professional" phagocytes of bone marrow origin (35). These cells of humans and other species that produce endogenous pyrogen include polymorphonuclear leukocytes (24, 30, 33, 150), monocytes (31, 34), tissue macrophages (8, 88), and phagocytic cells of the reticuloendothelial system (8, 64). Cells with a more limited ability to phagocytose material do not appear to produce endogenous pyrogen (35). Endogenous pyrogen produced by human polymorphonuclear leukocytes has been shown to be chemically and biologically distinct from that produced by human monocytes (65). Lymphocytes may be involved indirectly, by stimulating monocytes or macrophages to release endogenous pyrogen in certain febrile states accompanied by delayed hypersensitivity reactions (7, 9, 10, 46). It is noteworthy that the cells that are demonstrated to produce endogenous pyrogen also have a major role in many other features of immune response to foreign stimuli, both processing and reacting to such materials.

In addition to its presence in infection, fever has been associated with certain solid and lymphoid origin neoplasms (36, 128, 145, 157, 162, 188) as well as premalignant states (224). It has not been clearly established whether the temperature elevations in such a setting are produced by release of pyrogens from neoplastic tissue or from normal tissues, stimulated by the neoplasm or by factors released by the neoplasm (32, 194). Pyrogen production may be related to involvement of the lymphoid organs in Hodgkin's disease, with monocytes being the most likely producer (32), and with production being greater with early stage disease.

Humans have several mechanisms to control the extent of febrile response, as reviewed else-

where (108, 202). The clinician's decision about the advisability of suppressing fever is not a simple one. There is minimal danger from relatively high temperatures in most patients, and the febrile response may benefit the host both by direct effects and by guiding medical management of the illness (108, 197). Standard antipyretic treatments are not without their own adverse effects (108, 197). For example, aspirin (acetylsalicylic acid) is a widely used antipyretic that has been associated with adverse effects on multiple organ systems. It may also have effects on the immune system (independent of effects on fever) in certain instances. For example, Crout et al. (56) reported that ingestion of aspirin by healthy human volunteers depressed the response of their lymphocytes to stimulation by mitogens in vitro during and for at least 12 h after therapy. There was no detectable correlation between the serum salicylic acid levels and the degree of responsiveness. This effect could not be demonstrated by another group (193), and its biological significance remains to be determined. Aspirin may be associated with decreased early killing of staphylococci when added to human polymorphonuclear leukocytes at a concentration of 25 mg per 100 ml in vitro, a level that can be achieved in plasma during therapy with high doses (12).

Studies have been carried out in the recent and remote past regarding the effects of fever, or hyperthermia, on immune defense. Several qualifications must be kept in mind in reviewing the studies. First, data from investigations of hypothermia do not necessarily apply in the converse to hyperthermia. Second, the relationship of responses of the poikilothermic animals used in many experiments to the responses of humans is not firmly established. Third, and more specifically, mice, rats, and guinea pigs remain afebrile or become hypothermic in response to infections or inflammatory challenge (21, 90, 117), so that data regarding effects of fever on immune responses in those animals must remain suspect as applicable to humans. Fourth, effects due to microwave-induced hyperthermia must be viewed with caution, since thermal effects and microwave effects per se are not adequately distinguished at present. Fifth, as noted above, the terms fever and hyperthermia are not truly synonymous.

BENEFICIAL EFFECTS OF HYPERTHERMIA

In Vivo Studies

Induced hyperthermia was used to treat syphilis (190), gonococcal infections including endocarditis (22, 96, 220), and pneumococcal meningitis (184) in the pre-antibiotic era. Many studies were small and uncontrolled, but suggested benefit from the elevated temperatures. For example, treatment of gonococcal endocarditis in one case resulted in sterilization of the blood and sterilization and healing of the endocardial vegetations examined at necropsy, after death due to other causes (220). No pathological changes were noted in viscera that could be attributed directly to fever therapy. A second case of probable gonococcal endocarditis with acute gonococcal arthritis showed prompt recovery with fever therapy. Simpson and Kendell (190) reported results of treatment of early syphilis in 34 patients, using artificial fever and chemotherapy (heavy metals). There was a high failure rate with either modality alone in control groups. Addition of fever therapy was judged to greatly intensify curative action of the chemotherapy. In fact, lesions progressing in spite of chemotherapy began to heal with addition of fever therapy. More recently, Weinstein et al. (216) reviewed survival and factors influencing prognosis in 28 cases of spontaneous bacterial peritonitis. The presence of fever (with temperatures greater than 38°C) was associated with significantly diminished mortality in their patients. They speculated that body temperature elevation could be correlated with better function of host defense mechanisms.

In general, although some patients appeared to benefit from fever therapy during the period of its use, the effects were often insufficient to ensure survival (22). Thus, hyperthermia was abandoned as a therapy for infectious diseases with the advent of the antibiotic era. Establishing criteria of infection and examining the many variables involved remained problems for those investigating the effects of hyperthermia on humans.

Recent clinical interest in hyperthermia has been related to therapy of neoplastic disease. Adverse effects of hyperthermia on neoplastic tissue of patients, with relative sparing of normal tissue, have been demonstrated with hyperthermia alone (45, 91, 120, 160, 212) or hyperthermia in combination with irradiation or chemotherapeutic agents (129, 160, 195, 196). Measurements of immune functions during hyperthermia therapy are limited. Spontaneous regression of human malignancies has been reported after episodes of fever and infection (71). Stehlin et al. (196) suspected that effects of hyperthermia might be mediated in part by immune responses of the host. They noted regression and disappearance of distant metastases in some patients after hyperthermic chemotherapeutic perfusion

of a melanoma lesion of an extremity. Others suggested that the prognosis of patients undergoing resection for colorectal carcinoma may be improved, in less advanced carcinomas, if there was an increase in body temperature in the postoperative period (84). The possibility that such effects are mediated by immune responses should be considered.

Many studies regarding fever and host defense against bacterial infections have involved animals maintained at varying ambient temperatures and challenged with bacteria. Hyperthermia has been associated with increased resistance to pneumococci, staphylococci, and anthrax bacilli (22). Rich and McKee (169) infected rabbits with several strains of pneumococcus, including virulent type III strains that did not produce fatal disease at higher temperatures (41°C). These strains produced a primary local lesion at the site of the injection, and the regression of this lesion coincided with onset of fever in the infected rabbits. Subsequent injection site lesions showed marked restriction and faster regression. Artificially induced fever was similarly protective. The pneumococcal strains used were shown to be sensitive to the febrile temperatures of the rabbit, exhibiting changes in their capsule. Limited experiments by the above investigators using leukopenic rabbits suggested participation of immune responses in resisting the infection. The effect of fever on pneumococcal infection of rabbits was shown by others to be abolished by cooling the animals, using either manipulation of the ambient temperature or drug therapy (148). Survival of the animals paralleled the magnitude of the febrile response.

Kluger and co-workers (113), using the poikilothermic lizard *Dipsosaurus dorsalis*, studied the effects of fever on survival after challenge with *Aeromonas hydrophila*, a gram-negative bacterial pathogen of these animals. The poikilothermic lizards have a preferred body temperature, 38.5 to 39.0°C, which they maintain by selecting and moving to areas of appropriate ambient temperature. The lizards develop a 2°C fever, by this behavioral means, after injection of killed *A. hydrophila*. The effects of normal, low, and elevated temperatures on survival after live bacterial challenge were studied by using constant-temperature chambers, providing no opportunity for the animals to select alternate or preferred ambient temperatures. The mortality of the animals was inversely related to temperature, with the greatest survival evident at temperatures in the febrile range for the animals. Since the in vitro bacterial growth rate was stable over most of the temperature range studied, the investigators felt that enhanced survival at the elevated temperatures could be attributed to enhanced host defense mechanisms. Effective antipyretic therapy of the animals eliminated the enhanced survival with the infection. The elevation in body temperature did not have to be continuous to have significant beneficial effect (26). Investigations into mechanisms by which fever might enhance survival showed greater local inflammatory responses to injected bacteria in febrile lizards, as well as a quantitatively lower degree of dissemination of bacteria to other tissues (25). Local containment of infection by host defenses appeared to be enhanced by fever.

Whether the above data can be related to effects of fever in humans is not known, but these and other investigators have shown similar effects of fever in diverse higher vertebrates, including mammals (27, 54, 57, 111, 207, 208). For example, rabbits that developed low-grade fever after infection with *Pasteurella multocida* were shown to have decreased survival as compared to rabbits that developed high fever (208). With still greater fever, survival again decreased (111). Growth of the bacteria in vitro was not significantly different at the normal and febrile temperatures. There may be an optimum febrile range for an animal to resist infection, with moderate fevers beneficial and absence of fever or presence of marked fever detrimental. Covert and Reynolds (54) have shown that fever enhances survival, from bacterial challenge, of the goldfish *Carassius auratus* at temperatures that are above normal for this animal, yet are about 10°C lower than temperatures of the lizard, *D. dorsalis*. It appears that absolute temperature itself is not as important as is the elevation of temperature above that normal for the species, that is, the presence of fever.

Using animal models, notably newborns of different species, investigators have shown a beneficial effect of fever or hyperthermia on responses to viral infection. Newborn puppies are unable to regulate body temperature and produce a febrile response to infectious agents until they are 2 to 3 weeks old. The optimal range for multiplication of canine herpesvirus is below the normal rectal temperature of the mature dog (102°F) (42). In newborn pups, the infection is fatal without maternal antibody protection; in dogs older than 2 weeks, the disease is mild and often limited to the upper respiratory tract. The infection with this virus, studied in newborn animals, is quite similar to primary herpetic infections of newborn human infants, commonly associated with dissemination and high mortality (182). Carmichael et al. (43) challenged newborn puppies with canine herpesvirus

and controlled the animals' body temperatures by manipulating the ambient temperature. Pups kept at 82 to 86°F (with rectal temperatures from 95 to 98.5°F) all died 5 to 8 days after inoculation with virus and had widespread macroscopic and microscopic necrotic lesions characteristic of the infection. Viral antigen was detected by immunofluorescent staining in the lesions. In contrast, pups kept at 98 to 100°F (with rectal temperatures from 101.5 to 103°F) all survived 9 days or longer and had greatly reduced severity of pathological lesions compared to those observed in the natural puppy disease. Even the pups dying on days 9 and 10 showed greatly reduced viral antigen in lesions compared to animals maintained at the lower temperatures. Viral antigen could not be detected in any tissue of the pups sacrificed 16 and 21 days after infection. The frequency of virus isolation and the virus titers of the pups maintained at elevated body temperatures were markedly lower than those of the pups maintained at normal puppy temperatures at any point in time.

Newborn piglets were shown by other investigators to be more resistant to infection with attenuated transmissible gastroenteritis virus when maintained at high temperatures (76). This effect was attributed to a decreased rate of virus propagation in the bodies of the infected animals. Piglets kept at normal temperatures (20 to 23°C, with body temperatures of 36 to 38.5°C) had virus detectable in respiratory and lymphatic tissues. Virus could not be isolated from any of the tissues of piglets kept at the highest temperatures (35 to 37.5°C, with body temperatures of 37.5 to 41°C). The optimal temperature for growth of the virus in cell culture ranged from 30 to 40°C, so that a direct effect of higher temperature on virus growth was not likely to account fully for the effect. Immune responses of the animals were not examined. Further studies (185) with a virulent transmissible gastroenteritis virus strain, in pigs 2 to 3 months old, showed increased resistance of the pigs to induction of disease when they were maintained at high ambient temperature.

Mice have been shown to be more resistant to herpes simplex (179), poliomyelitis (131), and coxsackie B virus (211) infections at higher temperatures, even when elevated temperatures were produced 24 h or more after infection. Armstrong (5) demonstrated that inoculation with herpesvirus of mice that were held at laboratory room temperature was almost always fatal. However, infection of the mice was almost completely prevented by elevation of the body temperature of the mice by exposure to elevated ambient temperatures. Furthermore, protection by the higher ambient temperature was observed even when the temperature was elevated only during the day, with return to ordinary room temperature at night. This observation is similar to that of the studies with lizards and bacterial infection noted above.

Bell and Moore (19) studied effects of high ambient temperature (35°C) on rabies virus infection in mice. Elevated body temperature during the incubation period of the infection was associated with decreased mortality and frequent abortive infections. Elevated temperature produced late in the incubation period had similar effects and delayed the onset of illness. Temperature elevation produced after the onset of apparent illness had no effect on the course of the infection. When temperature elevation was delayed until 6 days after inoculation and then maintained for 7 days, disease and mortality were less than in control mice. However, a second (delayed) wave of infections was evident in surviving members of the group returned to normal ambient temperature. Thus, the mice were not completely free of active virus. Heat had been shown to have direct adverse effects on rabies virus in tissue culture, and this, at least in part, might have been the mechanism of the effects seen in this animal model. Enhancement of survival of a fish (*Oncorhynchus nerka*) during a viral disease by elevation of the water temperature to febrile levels has been reported by Amend (3, 4). This effect was not a result of virus destruction by the higher temperature; furthermore, the carrier state was not always eliminated.

Szmigielski et al. (205) demonstrated in vitro and in vivo inhibition of virus multiplication by microwave hyperthermia. Herpesvirus-infected cell cultures produced markedly lower virus yields at levels of hyperthermic therapy that had no detectable adverse effect on cell viability. Mortality due to herpes encephalitis after intranasal inoculation of mice was reduced by daily exposure to microwave hyperthermia from the time of infection onward. When hyperthermia was delayed for as long as 4 days after virus inoculation (to a time by which approximately 60% of the mice had succumbed to the infection), the mortality in mice still alive at the time was again significantly reduced. Microwave hyperthermia applied immediately after intravenous inoculation of mice with vaccinia virus resulted in a significant decrease in number of specific tail lesions that developed in the mice.

Bennett and Nicastri (22) reviewed data pertinent to fever and mycobacterial infections and presented evidence leading to reasonable speculation regarding a role for elevated tempera-

tures in defense against leprosy. They noted the fact that *Mycobacterium leprae* are profusely distributed throughout the body despite the fact that most tissue injury is confined to anatomical sites that have a lower temperature than internal organs. Many mycobacteria grow well at temperatures in the 30 to 33°C range, but poorly or not at all at 37°C. The authors speculated that the local temperature might determine the extent of tissue damage in leprosy, though perhaps not affect the survival of the organism. Extending this concept, it may be that the area of tissue injury is inversely related to the early cellular immune response produced to localize the infection and that this response is more effective at the higher temperatures of the internal organs. Early containment of infection by macrophages or other leukocytes, before extensive involvement of parenchymal tissue, might result from higher temperatures (see below). In fact, Bennett and Nicastri noted the frequent observation that febrile crises were followed by transient amelioration of symptoms and regression of lesions (147, 173), despite a lack of benefit in limited trials of fever therapy (147).

There are limited data regarding the effects of temperature on fungal infections. Cryptococci kept in vitro at 103°F were rapidly killed (114) and, when inoculated into rabbits that developed such a temperature, were relatively avirulent (115). In other studies, mice died consistently after inoculation with cryptococci except in those cases in which ambient temperature was manipulated to raise body temperatures to greater than 102°F (116). However, no benefit was apparent in two patients with cryptococcal infection treated with artificial fever (110).

The effects of temperature on responses to noninfectious challenge have been investigated using burn and other traumatic injuries. Mortality of unacclimatized hairless or shaved mice after burn or tourniquet trauma was reduced by elevated ambient temperature (31°C), relative to normal ambient temperature (25°C) (139). The beneficial effect of the higher temperature was also noted (although not statistically significant) in mice with normal fur. Burned germfree mice with normal fur also had a lower incidence of late mortality at the elevated temperature. Rats subjected to burn trauma and kept at a high (30°C) ambient temperature maintained positive nitrogen balance and had no mortality. In contrast, rats kept at a low (20°C) ambient temperature developed negative nitrogen balance and 60% late mortality (41). The burn wounds healed significantly faster at the elevated temperature. Such an effect was evident with fixed preburn diets, but was less evident with free access to food. Other studies of burn- and tourniquet-induced shock in mice have demonstrated increased mortality at ambient temperatures above or below 18 to 25°C (23, 70).

Much of the recent literature regarding effects of hyperthermia has pertained to neoplastic diseases. Hyperthermia has been shown to adversely affect neoplastic tissue more than normal tissue (45, 48, 78, 104, 152, 180, 181). This effect of hyperthermia on neoplasms has been reported with tissue culture systems (77, 154, 186, 217), with experimental animal tumors (61, 62, 83, 146, 152), and with human tumors (45, 91, 120, 160, 212). Hyperthermia has also been demonstrated to enhance the effects of irradiation or chemotherapeutic agents on malignant cells in tissue culture systems (20, 80, 87, 102, 122, 130), with experimental animals (63, 83, 85, 87, 153, 222, 223), and with human tumors (129, 160, 195, 196). Hyperthermia may in fact be most successful against cells in solid tumors that show the greatest resistance to standard irradiation or chemotherapy regimens (86). Several aspects of hyperthermic potentiation of antineoplastic regimens have been reviewed recently (52, 119). Mechanisms of direct hyperthermic effects on neoplastic tissue have been discussed in these and numerous other recent articles and will not be reviewed here.

It is difficult to separate direct from indirect effects of hyperthermia on neoplastic tissue in the in vivo setting. The data available from in vivo studies regarding effects on immune function are quite limited. While failure of initially surviving neoplastic cells to maintain growth after hyperthermic treatment may be due to an inability to repair sublethal damage, the contribution of host factors by destruction of remaining tumor tissue may play an important role (61). The possibility exists that an important effect of hyperthermia on neoplastic tissue is indirect in the in vivo setting, via stimulation of immune defense mechanisms. Such an indirect effect might then act synergistically with the direct effects of hyperthermia on neoplastic tissues. Attempts to correlate in vivo effects on tumor with effects on immune function were made by DeHoratius et al. (59). They reported assays of leukocyte function of three of their cancer patients undergoing hyperthermic therapy (two receiving concomitant chemotherapy), as well as the clinical responses of the patients. Total leukocyte counts were increased with hyperthermic therapy. Cells forming rapid rosettes with sheep erythrocytes (as a marker of certain T lymphocytes) were increased both in percentage and absolute numbers, although total T-cell numbers were unchanged. The C3 component of

complement was decreased after hyperthermic treatment. A depression of antibody-dependent lymphocyte- and polymorphonuclear leukocyte-mediated cytotoxicity was observed but, as the authors noted, anesthetic agents may have affected these assays. No changes were noted in immunoglobulin levels or other markers of T and B lymphocytes. Lymphocyte transformation responses to stimulation by mitogens were increased in two of the three patients. Clinical response to hyperthermia was variable in the three cancer patients: one had a temporary remission (8 months), another became free of detectable tumor by 7 months, and the third was palliated (and had internal tumor masses that could not be accurately measured). The first two patients, with malignant melanomas, were reported to show marked regression or disappearance of measurable lesions.

The proper role of fever or hyperthermia in the response to neoplasia or as a therapeutic approach in its treatment requires further study, especially investigations in human malignancy that include proper and adequate controls. Methods of inducing hyperthermia, current knowledge of its role, and the questions that have arisen have been extensively reviewed (52, 60, 92, 142, 151).

Assays of Immune Function

Artificial fever therapy in humans has been reported to cause leukocytosis of varying degree, with both a relative and an absolute increase of polymorphonuclear leukocytes and a decrease in lymphocytes (49). Phagocytic leukocytes are major effector cells of both early and late host defense against invading microorganisms. Many investigations have been concerned with the effects of temperature variation in vitro on the function of these cells. Although Phelps and Stanislaw (161) found little effect on human polymorphonuclear leukocyte motility over a wide range of elevated temperature (98 to 105°F), others have noted enhancement by hyperthermia. Nahas et al. (149) reported steadily increasing motility of human polymorphonuclear leukocytes with increasing temperature (from 6 to 42°C). Maximum motility was recorded at 42°C, and the hyperthermic (42°C) motility was significantly greater than that at 37°C. Bryant et al. (40) noted increasing human leukocyte motility as temperature was increased from 25 to 40°C, with an increase in motility of approximately 10% per degree centigrade. Again, motility at 40°C was significantly enhanced relative to that at 37°C. Rabbit polymorphonuclear leukocyte net surface charge (zeta-potential) and transmembrane potential have been reported to be relatively sensitive to temperature variation, with phagocytosis and exclusion of trypan blue dye less sensitive (165). With a decreased zeta-potential at higher than normal body temperature, a correlative increased tendency for polymorphonuclear leukocytes to adhere might have a favorable effect on host defense.

Ledingham noted enhanced uptake of *Staphylococcus aureus* by polymorphonuclear leukocytes at 43°C, relative to 37°C, at 15, 30, and 45 min after mixing the bacteria and leukocytes (118). Mandell (136) and Craig and Suter (55) found no difference over the temperature range of 36 to 40°C in phagocytosis and killing, respectively, of staphylococcus by human polymorphonuclear leukocytes. Peterson and co-workers (158, 159) noted depressed phagocytosis by human leukocytes at 41°C, whereas Ellingson and Clark (69) noted optimal phagocytosis of staphylococci between 38 and 40°C. Roberts and Steigbigel (171) noted enhanced bactericidal capacity of human polymorphonuclear leukocytes against *Escherichia coli, Salmonella typhimurium,* and *Listeria monocytogenes* at 40°C compared to 37°C. There was no difference between the temperatures in assays using *S. aureus.* Enhanced bactericidal capacity of human monocytes at the elevated temperature was not observed. Sebag et al. (183) found that hyperthermia increased killing of pneumococci but decreased the killing of *E. coli* by human leukocytes.

Bhatti et al. (28) studied reactivity of leukocyte cultures of patients with genitourinary malignancy to unheated and heated extracts of allogenic carcinoma. They used an antigen-induced leukocyte adherence inhibition assay and found that the in vitro reactivity of the leukocytes was greater when cultured in the presence of the heated tumor extracts. They speculated that exposure of cryptic tumor antigens to sensitized leukocytes might be one explanation of the greater response to heated extracts. The phenomenon described is likely to represent an effect of hyperthermia on immunogenic material rather than an effect on cell-mediated immune function. The effects of hyperthermia directly on cell-mediated immune functions have been investigated only recently.

The responses of lymphocytes to antigenic and mitogenic stimulation in vitro have been assayed in several studies. Ashman and Nahmias (6) noted significantly enhanced mitogen stimulation of human lymphocytes on days 2 and 3 of cultures at 39°C compared with cultures incubated at 37°C, with no difference in viability of the leukocytes at the two temperatures. Roberts and Steigbigel (171) found consistent and

significant enhancement of responsiveness of human mononuclear leukocytes at 38.5°C relative to 37°C with mitogen and antigen stimulation. Augmentation of response was not accompanied by acceleration of response. They noted no enhancement of transformation response at 40°C compared to 37°C; however, this may have been due in large part to decreased viability of the cells cultured in vitro at 40°C, as assayed by cellular exclusion of trypan blue dye. Smith et al. (192) studied human lymphocyte responses to mitogens and allogenic lymphocytes and found enhanced responses at 40°C compared to 37°C. They noted no difference in cell viability at the two temperatures.

Manzella and Roberts (137) examined the effects of hyperthermia (38.5°C) on resistance of human mononuclear leukocytes to the adverse effects of exposure in vitro to influenza virus. Exposure to this virus at 37°C had previously been shown to depress the lymphocyte transformation response to mitogen (172). In the studies with virus, leukocytes, and hyperthermia, enhancement of responsiveness by hyperthermia (171) and depression by influenza virus exposure were again observed. Furthermore, it was noted that hyperthermia significantly counteracted the adverse effects of virus exposure on leukocyte mitogen responsiveness. Whereas cells exposed to virus and incubated at 37°C showed significantly depressed mitogen responsiveness, cells exposed to virus and incubated at 38.5°C did not differ from the control cells (not exposed to virus) that were incubated at 37°C.

Smith et al. (192) noted enhancement of human cytotoxic T-lymphocyte responses at 37°C when sensitization at 40°C incubation was compared to sensitization at 37°C. Sensitization at 37°C followed by parallel cytotoxicity assays performed at 37 and 40°C showed no difference in cytotoxicity.

In the studies of rabbits challenged with pneumococci (169) cited earlier, the bacteria were observed to disappear when clumps of leukocytes had accumulated in the tissues. Phagocytosis occurred as the bacteria lost their capsules. In the lizard model, also cited earlier, infected febrile animals did have less dissemination of bacteria after inoculation, and this was associated with a greater leukocyte accumulation at the site of inoculation (25). The possibility existed that fever produced greater chemotactic attraction of leukocytes to the inoculation site or greater inhibition of leukocyte migration away from the site after the cells had arrived. The temperatures used in the lizard model could not be shown to have an effect on in vitro random migration or chemotaxis of granulocytes from that animal (25). However, the possibility remained that fever, or hyperthermia, could have enhanced production of or response to a lymphokine such as leukocyte migration inhibition factor (LIF). This possibility was investigated by Roberts and Sandberg (170), using human leukocytes and a hyperthermic temperature (38.5°C) previously shown to enhance human leukocyte transformation responses to different stimuli (171). Leukocyte migration was assayed, using an agarose plate method, at both 37 and 38.5°C after exposure of the leukocytes to LIF-containing or control leukocyte culture fluids produced at 37 or 38.5°C. Hyperthermia (38.5°C) was consistently associated with greater spontaneous and greater stimulated LIF production by the human mononuclear leukocytes, as well as decreased spontaneous leukocyte migration and greater inhibition of leukocyte migration by a given amount of LIF. Leukocyte migration at 38.5°C after exposure to LIF produced at 38.5°C was greatly reduced relative to migration at 37°C in response to LIF produced at 37°C. The results were similar with mitogen- and antigen-stimulated LIF. In rabbits, elevation of body temperature by exposure to a high ambient temperature has been shown to result in increased production of interferon, another immune mediator, after injection of virus although not after injection of endotoxin (163).

Many studies of the effects of temperature on humoral immunity have used poikilothermic animals and stimulation with antigenic material. Temperature has been shown to affect immune responses of fish and other poikilothermic animals (13, 97, 127), as measured by antibody response or rate of destruction of integument grafts, with optimal temperature levels being specific for different species. Antibody production by fish could occur after long periods at either high or low temperatures if immunological memory was established at high temperatures (13). Ipsen (101) demonstrated that antibody production by mice could be more effective at an elevated body temperature. After immunization with tetanus toxoid at normal, hypothermic, and hyperthermic temperatures, with subsequent challenge with toxin at room temperature, the greatest immune response was seen in animals immunized at the elevated temperature. The difference in response was most distinct as the immunizing toxoid dose was lowered.

Attempts to immunize mice to herpesvirus were described by Armstrong (5) as part of his studies on effects of temperature discussed above. When inactivated virus was used to inoculate the animals, no immunity developed. When active virus was used in sufficient dosage

to produce immunity, the mice usually died. In contrast, animals inoculated with active virus while being held at high ambient temperatures usually developed no symptoms but tended to develop immunity toward reinoculation.

Microwave or radiofrequency irradiation has been a major method of inducing both generalized and localized hyperthermia for treatment of neoplastic tissue. In many of the studies on microwave effects, especially in vivo, varying conditions of irradiation have been used, often with sufficient power density that thermal effects cannot be separated from those possibly due to the microwaves per se. This variation in application of microwaves may also account for much of the diversity in data regarding effects of such treatment on components of the hematopoietic system (15). Thus far, experiments on the effects of microwave exposure on human lymphocyte cultures are inconclusive, but they suggest that exposure (without detected heating) induced blastic transformation of the lymphocytes and release of factors into the culture medium that inhibited mouse macrophage migration (199, 200). Microwave radiation of mouse spleen cells in vitro, with minimal changes in temperature of the cultures detected immediately after irradiation, caused no consistent difference in the blastogenic response of splenic lymphocytes to mitogen stimulation (191).

In studies of local microwave-induced hyperthermic treatment of tumors in rats, increased reactivity of T-lymphocyte and macrophage systems was noted (204). Enhanced nonspecific (increased production of bovine serum albumin antibodies, high reactivity of spleen lymphocytes to phytohemagglutinin, increased serum lysozyme levels) and specific (increased cytotoxicity of lymphocytes and macrophages to cultured tumor cells and higher reactivity of lymphocytes to mitomycin-inhibited tumor cells) immune responses were reported. Microwaves have been reported to induce an increase in the frequency of complement receptor-bearing lymphoid spleen cells in mice (219). Although the significance of this is not fully assessed, such a change may represent a maturation of B lymphocytes to a stage with expression of an activation structure. Rectal temperature differences (before and after exposure) reported were small, but a thermal effect within a range that might normally be managed and dissipated by the animals could not be excluded.

ADVERSE EFFECTS OF HYPERTHERMIA

In Vivo Studies

Prolonged fever can be associated with adverse effects on the host (17, 38, 107). Fever may result in increased heart rate deleterious to individuals with compromised cardiovascular function and may result in convulsions, generally an effect limited to young children. Both anabolic and catabolic responses are stimulated by fever, but the latter are usually greater in magnitude and produce the prominent features of the febrile state. Basal metabolic rate is increased approximately 7 to 8% for each degree Fahrenheit of temperature elevation. Negative nitrogen balance ensues, often accompanied by mild to severe dehydration. Albuminuria and electrolyte losses may develop, and losses of trace elements parallel nitrogen loss. Intestinal absorption of iron may decrease, although this change may be a defensive maneuver on the part of the host (215). These metabolic changes have been demonstrated in diverse infectious and inflammatory processes and with artificial fever induction in normal volunteers (18). Fever can affect the metabolism and pharmacokinetics of chemotherapeutic agents (see below).

Atwood and Kass (11) investigated the relationship of temperature to the lethal action of bacterial endotoxin in animals. Earlier studies in their laboratory had shown increased lethality at elevated temperatures, but used animals that generally responded to endotoxin by becoming hypothermic. Atwood and Kass used rabbits, which, like humans, become febrile when challenged. They showed that fever increased the susceptibility of the rabbits to lethal actions of endotoxin. Mice were shown to have increased susceptibility to streptococcal infection when maintained at elevated temperatures (50, 117). Contrasting observations have been reported by other investigators (see below).

"Fever blisters," due to recrudescence of herpes simplex infection, are very common during many but not all infections causing fever (106, 203). Recurrence of herpetic lesions has been reported to occur frequently during artificial fever therapy (213). Elevated temperatures have been associated with shortened incubation periods and increased severity of lesions of herpesvirus infection in sea turtles (89). This observation may have represented an example of heat stress induction of a latent herpesvirus infection.

Assays of Immune Function

Peterson et al. (159), in the studies cited above, noted depressed phagocytosis of staphylococci by human polymorphonuclear leukocytes at a hyperthermic temperature. They felt that the depressed in vitro phagocytosis observed at 41°C compared to 37°C resulted from decreased attachment of bacteria to leukocytes as well as decreased bacterial ingestion, with opsonization remaining normal at 41°C (158).

Sebag and colleagues (183) found that hyperthermia increased killing of pneumococci but decreased the killing of *E. coli* by human leukocytes. In examining the effects of temperature on killing by serum (without leukocytes), a serum-resistant organism was not killed by serum alone at any temperature tested. Early killing (by serum alone) of a serum-sensitive organism was not affected by temperature level, but later killing was greater at 37°C than at 39 or 41°C. At the latter temperatures no further activity of the serum was noted.

The function of murine cytotoxic T lymphocytes has been reported to be affected adversely by high degrees of hyperthermia (42 to 44°C) in vitro, with the effect proportional to the temperature attained and duration of exposure (132). Cytotoxic cells present after 7 days of a mixed leukocyte culture were more sensitive than cells present after 4 days, with cells at 11 days being more sensitive than either of those populations. Others have reported similar effects of in vitro heating (43°C) on cell-mediated cytotoxicity (93). Cell viability, as determined by dye exclusion, was largely intact relative to changes in cytotoxic activity (132). Decreased cell viability has been related to both degree of hyperthermia and duration of exposure in vitro by other investigators (171). Similar degrees of hyperthermia in vivo may not cause adverse effects on this immune function, and lesser degrees of hyperthermia either in vivo or in vitro have enhanced cytotoxic function. For example, Smith et al. (192) noted enhancement of human cytotoxic T-lymphocyte responses at 37°C when sensitization at 40°C incubation was compared to sensitization at 37°C. Sensitization at 37°C, followed by parallel cytotoxicity assays performed at 37 and 40°C, showed no difference in cytotoxicity. The potential differences between effects of in vivo and in vitro hyperthermia were illustrated by the studies of Schechter et al. (178). They noted that rat spleen cells specifically sensitized to a tumor and heated in vitro at 40.5°C for 1 h exhibited a diminished capacity for cell-mediated cytotoxicity. In contrast, heating tumor-bearing rats (in vivo hyperthermia) to a similar degree did not affect spleen cell-mediated cytotoxicity toward specific tumor cells, as tested in a subsequent in vitro assay.

Effects of microwave-induced hyperthermia are of interest, although microwave and thermal effects are often difficult to separate. Radiofrequency radiation-induced hyperthermia in mice was associated with transient lymphopenia with a relative increase in splenic T and B lymphocytes and with decreased in vivo local delayed hypersensitivity to sheep erythrocytes (123, 125). The latter response was not affected by a comparable increase in core temperature produced by warm air. Serum corticoid levels were severalfold higher in the radiofrequency-exposed animals than warm-air-treated or control animals, and steroid administration to the latter two groups produced findings similar to those noted in the radiofrequency-exposed animals. Thermogenic microwave stress of mice was also reported to be associated with steroid release and immunosuppression of the allograft response (124). Allograft rejection was delayed in the whole body microwave-treated animals who developed an increase in core temperature, but not in animals exposed to nonthermogenic microwave treatment prior to allograft challenge.

BENEFICIAL EFFECTS OF HYPOTHERMIA

In Vivo Studies

Most studies of effects of hypothermia on host defense in humans have been directed toward treatment of sepsis with associated shock. The studies have generally involved small numbers of patients with inadequate controls. (Studies of hypothermic therapy for surgical procedures will not be reviewed here.) The greatest benefit from hypothermia was reported in patients with neurological lesions due to infection, and clinical improvement was probably related to decreased cerebral edema rather than a beneficial effect of hypothermia on the infectious process itself (109).

Reeves and Lewis (166) did report on critically ill patients that were randomized into control or hypothermic (35 to 36°C) groups after failure of conventional treatment for the causes of their fever. The causes of fever were not specified, but were noted either as nonsurgical complications or, in the majority of patients, as complications following surgery, including neurosurgery. There were only 13 patients in each group: there were three survivors and eight with clinical improvement in the cooled group, with no survivors (three with some clinical improvement before death) in the control group. Again, it must be noted that the complications being treated were not specified. Whereas other studies on effects of hypothermia specified both infectious and noninfectious processes, those studies did not include adequate controls.

Prolonged survival without a decrease in mortality was observed in dogs treated with hypothermia for fecal peritonitis (29). Septic shock occurred in hypothermic and control dogs within 3 h after instillation of the feces. Blood cultures were positive during hypothermia, but no quantitative increase in circulating colony-forming

units of bacteria was noted in the cooled septic animals. Hypothermia was demonstrated to prolong survival in lethal pneumococcal peritoneal infections of mice and to increase survival with sublethal doses of invasive bacteria (67). The major protective action of hypothermia in this mouse model appeared to be a retarding of bacterial multiplication (68), with host immune defense mechanisms such as phagocytosis and antibody responses simultaneously depressed (see below). Pneumococci grown at the hypothermic temperatures either in vitro or in vivo were as virulent as those grown at 37°C, as judged by subsequent growth at 37°C and studies of lethality for mice (68).

ADVERSE EFFECTS OF HYPOTHERMIA

In Vivo Studies.

Hypothermia rendered mice more susceptible to lethal effects of gram-negative bacterial endotoxins (164). Cold-exposed mice were also shown to be more susceptible to challenge with bacteria such as *S. typhimurium* and *S. aureus* when strains of low rather than high virulence were employed (143, 164). Shortened survival time as well as decreased survival were noted with lowered temperature. In mice infected with salmonella, secondary deep tissue invasion by staphylococci was a prominent feature in the mice rendered hypothermic compared to those kept at normal ambient temperature. The secondarily invading staphylococci appeared to have a respiratory tract (nasal tissue) origin (144). Cold exposure (4°C) was shown to inhibit clearance of *Staphylococcus albus* and *Proteus mirabilis* from the lungs of mice, presumably due to effects on alveolar macrophage function in the early postinfection period (82).

Several dog model studies on the effects of temperature involved hypothermia and bacterial challenge (39, 72, 81, 214). These studies demonstrated decreased clearing of invasive bacteria from the bloodstream or injection sites with temperatures that were below normal for the dogs. Leukocyte functions were not assayed.

Transmissible gastroenteritis of pigs, although a highly contagious viral disease, was noted to occur mainly during colder months. In addition, experimental infections were resisted by the animals during the warmer summer months, but not during the winter months (185). In view of these observations, Furuuchi and Shimizu (76), in the study cited earlier, examined the resistance of newborn piglets to attenuated transmissible gastroenteritis virus at varying temperatures. Piglets held at temperatures below normal had greater early mortality, with increased frequency of virus recovery and markedly higher viral titers. In studies with the virulent virus strain, a sudden decrease in the ambient temperature (30 to 4°C), either before or after virus inoculation, caused a notable enhancement of the disease in 2- to 3-month-old pigs (185). Carmichael et al. (43), in another study cited earlier, examined responses to canine herpesvirus infection in naturally resistant older puppies (4 to 8 weeks old). Puppies with normal rectal temperatures (100.5 to 102°F) did not develop signs of illness due to the virus, and the virus was not isolated from their tissues at necropsy. Immunofluorescing viral antigen was found rarely in lymphoid cells. In contrast, the virus was readily isolated from many tissues, including liver and spleen, of pups whose temperature had been artificially reduced (94 to 97°F). The latter animals had many foci of immunofluorescing viral antigen. Resistance of adult mice to infection with coxsackievirus was shown by others to be markedly lowered by induced hypothermia (37).

Assays of Immune Function.

Hypothermia induced early leukopenia in dogs (53, 68, 94, 95, 209, 210), usually with a relative increase in percentage of lymphocytes (53, 94). This leukopenia could be reversed rapidly by rewarming, without a leftward shift of granulocytic leukocytes on reappearance (209). Some investigators felt that leukopenia depended on the degree of hypothermia. Earlier studies all involved temperatures below 25°C in the dogs. Hypothermia to 30°C in dogs was reported to be associated with normal leukocyte counts; counts started to decrease by 28°C and fell progressively as the temperature was lowered (29). Cases of hypothermic (32°C) therapy of humans were associated with leukocytic responses in the face of infection (29).

In studies discussed earlier, hypothermia was demonstrated to have adverse effects on leukocyte motility. Several authors noted depression of motility over the range of 6 to 36°C relative to 37°C, with lower temperatures having greater adverse effects (40, 149, 161). Human polymorphonuclear leukocytes were shown to lose their ability to form amoeboid shape, when in suspension in vitro, when the temperature was lowered to nonphysiological levels (4°C), perhaps correlating with functional integrity of the cells (126). Data were not reported regarding effects of elevated temperature on cell shape.

Reports of effects of hypothermia on phagocyte functions have apparently disagreed, due in large part to variations in methods utilized and temperatures assayed. Roberts and Steigbigel (171) noted no significant effect of a moderate degree of hypothermia (34°C) on bactericidal

capacity of human polymorphonuclear leukocytes or monocytes against *S. aureus*, *E. coli*, *S. typhimurium*, and *L. monocytogenes*. Mandell (136) noted equivalent phagocytosis of staphylocci by human leukocytes over a 33 to 37°C range, with a decrease evident at 24°C. Craig and Suter (55) reported depressed killing of staphylococci over 26 to 37°C, with the magnitude of depression directly related to the degree of hypothermia. Ellingson and Clark (69) noted equivalent uptake of staphylococci at 35 and 37°C with guinea pig leukocytes, with a slight decrease at 35°C relative to 37°C with human leukocytes. Ledingham (118) noted depressed leukocyte phagocytosis of staphylococci at 18°C, as well as a prolonged latent period preceding bacterial uptake. This he felt to be due primarily to depressed opsonization of the bacteria at the lower temperature. Fenn (74), analyzing the data of Madsen and Watabiki, reported progressively longer latent periods and lower maximum uptake of bacteria by leukocytes as temperatures were lowered from 35 to 5°C.

Two studies examined effects of hypothermia on lymphocyte transformation responses. Roberts and Steigbigel (171) noted no significant effect of minimal physiological hypothermia (36°C) on lymphocyte transformation response to stimulation with optimal doses of mitogen and antigen. Hirsch et al. (99) noted insignificant transformation responses of rat lymphocytes to mitogen between 4 and 30°C; assays at temperatures between 30 and 37°C were not reported.

Lowering the body temperature of rabbits by exposure to a low ambient temperature was shown to result in decreased production of virus-induced but not endotoxin-induced interferon (163).

Immunization with various antigens at low temperatures has been shown by many investigators to be ineffective, as reviewed by Avtalion et al. (13). Studies by Cone and Marchalonis (51) using marine toads suggested that the productive phase of the immune response could be critically sensitive to temperature, as measured by the appearance of circulating antibodies. Significant differences in the effects of lowered temperature on the humoral immune response have been shown to exist between species. This variability was reviewed and further established by Tait (206). He found the toad *Bufo marinus* to be capable of producing antibodies over the entire range of temperature at which it could survive, with temperature affecting the rate of antibody production but not the final titer produced. The time required to reach maximum antibody titer after immunization was increased as the temperature decreased. In contrast, the lizard *Egernia cunninghami* produced antibodies only over a very restricted temperature range. In the lizard, decreasing the temperature decreased both the rate of antibody production and the maximum titer produced.

Response of mice to an antigenic challenge was diminished by hypothermia, with effects persisting for a variable period after such treatment. This was demonstrated using assays of hemolysin response to intraperitoneal sheep erythrocytes (68).

TEMPERATURE VARIATION AND ANTIMICROBIAL AGENTS

Effects of fever, or hyperthermia, on activity of antimicrobial agents have been investigated to a limited extent and commonly in vitro rather than in vivo. Disinfectants such as chlorine were shown to be more germicidal as the temperature was raised (47, 140, 174). Sulfanilamide activity against streptococci was shown to be bacteriostatic at 39°C but bactericidal at 40°C in vitro (218). Consequences of such an effect have not been established in vivo, although Ballenger et al. (14) reported successful treatment, when the two modalities were combined, of a few cases of gonococcal infection that had not responded to either fever alone or sulfanilamide alone.

Eagle and Musselman (66) showed greater spirocheticidal activity of different concentrations of penicillin as the in vitro temperature was raised to levels in the febrile range for humans. The rate of spirocheticidal action was markedly enhanced by raising the temperature. In the absence of penicillin, the growth of the spirochetes was not adversely affected by temperature elevation over the 24 h of the assay. In vivo, the curative effect of penicillin for syphilitic rabbits was increased eightfold for animals subjected to a single hotbox hyperthermic treatment, according to Stokes's review (201) of further work by Eagle. Reynolds et al. (168) examined combined malarial fever therapy and penicillin in the treatment of human neurosyphilis and reported clinical improvement in 58% of treated patients compared to 46% of those receiving penicillin alone. They reported that improvement in spinal fluid abnormalities was more complete with the combined treatment.

In vitro studies of effects of temperature (19 to 37°C) on minimum inhibitory concentrations of penicillin and tetracycline against *S. aureus* PS/5 strain showed reduced efficacy of penicillin at the lower temperatures but enhanced efficacy of tetracycline at the lower temperatures, as assayed by both gradient agar plates and tube dilution methods (103). Minimal inhibitory and bactericidal concentrations of several antibiotics active against cell walls of *Streptococcus faecalis*

were tested at 30 and 37°C by Hinks et al. (98). Whereas penicillin and methicillin were more active at the higher temperature, cycloserine was more active at the lower, and vancomycin was equally active at both. Effects of temperature variation on the bacteria in the absence of antibiotics were not reported. The antibiotics involved have differing modes of action, and the significance of these observations is not known.

Other studies have demonstrated no consistent effect of 40°C incubation compared to 35°C on the growth of *S. aureus* and group A, B, and D enterococcal streptococci, or on the minimal inhibiting or minimal bactericidal concentrations of several bactericidal and bacteriostatic antibiotics for clinical isolates of those bacteria (138).

Investigations of the effects of fever on antibiotic levels in blood have produced varying results. Blood sulfanilamide levels after oral drug administration to rabbits were unaffected by fever except for a slower rise and longer maintenance of levels (121). The average maximum blood level was attained by 6 h in febrile animals as opposed to 3 h in those animals without temperature elevation. Pennington et al. (156) studied serum levels of gentamicin after intramuscular injection of the antibiotic into febrile and afebrile dogs and human volunteers. In their human subjects receiving etiocholanolone to produce fever, there were no differences in serum levels between control subjects and those who received etiocholanolone but did not develop fever. In contrast, there was a 40% average decrease in serum gentamicin concentrations in those subjects who developed fever after receiving etiocholanolone. Of note was the fact that there were no statistically significant differences in the renal clearance or half-life of the antibiotic. Serum levels were determined for up to 3 h and were declining after a peak at 30 to 60 min for both the febrile and afebrile subjects. Siber et al. (187) found that gentamicin half-life was shortened in febrile patients, and this change correlated with peak concentrations. Many of the effects of temperature variation on chemotherapeutic agents in vivo could be expected to be related to metabolic alterations produced in the host by the febrile state.

PROSPECTS AND CONCLUSIONS

From the studies reviewed here, it should be apparent that the role of fever in disease is complex and far from defined. However, many studies do suggest a survival value of fever with various insults, both infectious and neoplastic.

No established link exists between the ability of humans to develop fever and the ability to better withstand an infectious challenge. It is reasonable, though, to speculate that many of the observations from animal models would also pertain to human disease. For example, newborn animals are less able to control body temperature in response to an infectious agent and are better able to demonstrate a protective effect of fever in the controlled experimental setting, as reviewed above. In perhaps a similar way, both very young and very old humans are most at risk of mortality when infected with bacteria or viruses. These population groups, along with debilitated individuals of any age, are those least likely to show a significant febrile response in the setting of infection (2, 58, 100, 155, 167). Various studies have suggested that certain normal immune functions decline with age, to a variable extent according to the functions studied (75, 79, 105, 133–135). Likewise, in comparison with older children and young adults, defects in leukocyte functions and other factors involved in resistance to infection have been noted in neonates (73, 177, 198). It is tempting, though quite speculative, to suspect that a link between the lessened febrile and immune responses may be a factor contributing to the greater risk of mortality from infection in these individuals. It is, perhaps, just as likely that lessened febrile responses and lessened immune responses in these individuals are coincident indicators of a more basic characteristic.

It is also tempting to think that fever may represent a leukocyte-based amplification mechanism to affect host responses to challenge. For example, cell-mediated immune function appears to be important in resistance to viruses, with macrophages playing an important role (1, 44, 141, 189, 221). One could speculate that contact between host monocytes or macrophages and an invading organism such as a virus would result in release of endogenous pyrogens (8, 31, 34, 88). This might result in fever, amplifying the processing and presentation of that antigenic viral material to the lymphocytes (6, 171, 192). The lymphocytes may in turn stimulate macrophages to produce more pyrogens (7, 9, 10, 46) and may themselves, in the presence of fever, produce more lymphokines, including interferon (163, 170). The presence of fever might also enhance a virus-specific antibody response, similar to that observed with other stimuli (5, 13, 101). Virus multiplication may be directly inhibited, for some viruses, at febrile host temperatures (16, 44). The optimal temperature for virus-induced interferon production may be higher for certain viruses than the optimal temperature at which those viruses can replicate, as determined by plaque formation in cell cultures (176). Viruses with the highest optimal temper-

atures for growth in chick cells can also be the strains most resistant to the antiviral action of interferon and most virulent for chicken embryos (175). The increased production of interferon and other lymphokines in the febrile host might further enhance the virucidal activities of the host macrophages (1, 189). Thus, for certain viruses, host temperatures in the febrile range might have both direct and indirect effects on the invading virus.

Available data on effects of fever on immune functions are limited and occasionally in conflict. However, accumulated direct and indirect evidence tends to suggest an overall beneficial effect of moderate fever on host defense mechanisms. Common sense also argues for a beneficial role of fever, to assure its place over time and across species. Further investigations regarding the role of fever, especially its effects on immune defense mechanisms, appear to be warranted in view of these considerations. Except in certain cases, such as the patient with compromised cardiovascular function or the young child susceptible to febrile convulsions, it is quite possible that fever may be of benefit and antipyretic therapy may be a disservice.

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