PERGAMON

Journal of Thermal Biology 28 (2003) 1–13

Journal of
THERMAL BIOLOGY

www.elsevier.com/locate/jtherbio

Fever: pathological or physiological, injurious or beneficial?

Clark M. Blatteis*

Department of Physiology, College of Medicine, The University of Tennessee Health Science Center, 894 Union Avenue, Memphis, TN 38163 USA

Received 17 February 2002; accepted 19 June 2002

Abstract

Fever, the body's most manifest sign of infectious illness, is only one of a concatenation of complex, nonspecific host defense responses to infectious pathogens termed the acute-phase response. It develops in most endotherms via the activation of a combination of various autonomic and behavioral mechanisms. It also occurs in many ectotherms, most usually as the result of behavioral processes alone. Although fever may shorten disease duration and improve survival, antipyretic medications are nonetheless routinely prescribed, with apparently negligible adverse effects on the course and outcome of the disease. The popularity of antipyretics is probably due mostly to their moderating effects of the discomfort level and consequent alleviation of the anxiety of afflicted patients and/or their caregivers. But is treatment of fever really indicated? Would letting fever run its natural course be better? Recent data suggest that, while heat/fever may kill some pathogenic microbes, this would not seem to be its principal role. Rather, heat/fever would appear to serve an important adjuvant function by enhancing the effectiveness of certain selective, stimulus-activated adaptive immune responses and thereby helping to compartamentalize the acute-phase response to the infected site. But arguably even more important may be its temporal modulation of the stimulus-induced generation of TNFα, IL-1β and IL-6 early during the innate immune response, thereby obviating the risk of the potential harmful effects that could result from their dysregulated co-expression.

1. Introduction

"Humanity has but three great enemies: fever, famine and war. Of these, by far the greatest, by far the most terrible, is fever."

W. Osler, 1986. The study of the fevers of the South. JAMA 26, 999-1004.

"A fever supervening is favorable."

Hippocrates (460–357 BC).

Cited by J.R. Coxe, 1846. The writings of Hippocrates and Galen. Lindsay and Blakiston, Philadelphia.

"Fever is a mighty engine, which nature brings into the world for the conquest of her enemies."

T. Sydenham (1624–1689).

Cited by R.M. Yost, Jr., 1950. Sydenham's philosophy of science. Osiris, 9, 84–104.

Fever is defined in the current glossary of terms for thermal physiology (IUPS Thermal Physiology Commission, 2001) as "a state of elevated core temperature (T_c) … due to an elevation of the set-point of T_c … actively established and defended by … heat producing and heat-conserving thermoeffectors." Because fever occurs most commonly in association with infectious diseases, it has come to be regarded as the very hallmark

Abbreviations: AILD—angioimmunoblastic lymphadenopathy; ARF—acute rheumatic fever; CLL—chronic lymphocytic leukemia; CML—chronic myelogeneous leukemia; CV—cardiovascular; GI—gastrointestinal; GNB—Gram-negative bacteria; GPB—Gram-positive bacteria; IH—infectious hepatitis; ITP—idiopathic thrombocytopenic purpura; JRA—juvenile rheumatoid arthritis; MI—myocardial infarction; SBE—subacute bacterial endocarditis; SLE—systemic lupus erythematosus; TTP—thrombotic thrombocytopenic purpura; VD—veneral disease

*Tel.: +1-901-448-5845; fax: +1-901-448-7126.

E-mail address: blatteis@physio1.utmem.edu (C.M. Blatteis).

0306-4565/02/$ - see front matter
PII: S0306-4565(02)00034-7

of infection. However, although it accompanies many infectious diseases, it is not, in fact, an obligatory accompaniment in all cases, and its magnitude and duration also are not consistently correlated with the severity of the infection (Atkins and Bodel, 1979; Atkins, 1982). Fever, moreover, is not uniquely a sign of infection, as a regulated rise in T_c (as opposed to a passive [hyperthermic] rise) may also occur during noninfectious diseases, e.g., in certain autoimmune, neoplastic and granulomatous disorders, in vascular thrombosis and infarction, in stress, etc. (Table 1). This is so because various cytokines, the endogenous mediators of infectious fever, are also induced in the course of these diseases (Holtzclaw, 1995; Dinarello, 1996; Cannon, 2000; Dinarello and Pomerantz, 2001; Sirvent, 2001).

Fever, when it occurs, is often a frightening experience (see opening quotation by Osler), particularly to the

Table 1
Fever manifestation in various diseases of adult humans. Modified from Atkins and Bodel (1979)

Disease category	Usually prominent	Often present (± prominent)	Rare/absent
Infectious			
Acute	Septicemias (all microbes)	GPB—exotoxin formers (e.g., diphtheria, tetanus, clostridia)	Bacterial—local, superficial exc. Strept (erysipelas) (e.g., cholera, botulism, VD (local), cystitis, bacterial food poisoning)
	Local (all microbes) in most deep tissues, spaces, and organs	GNB—superficial (e.g., whooping cough, shiegellosis	Leprosy
		Tuberculosis	Mycoses (superficial)
		Mycoses (systemic)	"Cold", GI viruses
		Resp. viruses (exc. flu); IH	Amebiasis (GI)
		Viral gastroenteritis	Flukes, worms (exc. Migratory phases)
Chronic	SBE	Bacterial (any) esp. s.c. tissues, bone, etc.	Tertiary syphilis
	Chronic Mg′cemia		Slow viruses
Non-infectious			
Acute inflammatory (w/o infection or known allergy)	Multiple pulmonary emboli	Inflammatory bowel disease	
	Crush injury	MI	
	Acute gout	Alcoholic hepatitis	
	Acute cholecystitis	Acute porphyria	
	Pancreatitis		
	Appendicitis		
	Thrombophlebitis		
Tumors and blood dyscrasias	Acute leukemias (all)	Histiocytic lymphoma	
	Hodgkin's disease	Hepatoma; hypernephroma	CLL; CML; (exc. Blast crisis)
		Metastatic carcinoma (liver)	Carcinomas (most)
		Eosinophilic granuloma of bone	Benign tumors
		Ewing's sarcoma	Plasma cell dyscrasias (e.g., myeloma)
Collagen vascular disease	SLE	Polyarteritis nodosa	Scleroderma
	JRA	Giant cell arteritis	Dermatomyositis
	ARF	Wegener's granulomatosis	Chronic rheumatic syndromes (e.g., rheumatic arthritis, ankylosing spondylitis, etc.)
Hypersensitivity; granulomas (allergic, drug)	Serum sickness	Sarcoid	Asthma; hay fever; hivesl IgE-mediated anaphylactic reaction
	Blood transfusion reaction	AILD?	Acute/chronic glomerulonephritis
	Erythema nodosum; erythema	TTP?	ITP

Table 1 (*continued*)

Disease category	Usually prominent	Often present (± prominent)	Rare/absent
	multiforme		
			Primary biliary cirrhosis
Abscess	Any (w/access to circul)	Small or draining	"Walled off" or superficial
Noninflammatory			
	Heat stroke?	Delirium tremens	Most dermal diseases (exc. Pustulent psoriasis)
		CNS bleed	Endocr, metab, storagge diseases CV, pulmonary, GI, neurological disease (w/o inflam)
		Psychological stress	Cirrhosis (1° bil/Laennec-inact)
			Most coagulopathies
			Hematolodical disease (RBC), exc. Sickle cell anemia in crisis
			Most poisons

Table 2
Sickness behaviors typically elicited by infectious pathogens or their products

Fever
Hyperalgesia
Lethargy, somnolence
Anorexia, adipsia
Weakness, malaise
Decreased locomotor activity
Inability to concentrate
Loss of interest in usual activities, listlessness
Disappearance of body-care activities
Withdrawal

parents of sick children ("fever phobia" Barton and Schmitt, 1980; Kramer et al., 1985; Crocetti et al., 2001]), because it is attended not only by elevated T_cs, but also by other signs of "sickness behavior" (Table 2). These discomforting sensations can indeed be very alarming to both the patients and/or their caregivers because fever is interpreted by them not as defined by thermal physiologists, but rather as a syndrome indicative of a dangerous and potentially deadly illness (Iriki, 1988; Zitelli, 1991; Blumenthal, 1998). Since antipyretic therapy relieves to varying degrees these untoward signs, hence moderating the discomfort level and alleviating the associated anxiety, this recovery is associated in the minds of many as being directly related to the suppression of the elevated T_c. But, in fact, the restoration of apparent well-being occurs not because of the lowering of T_c per se but because most antipyretic drugs, and most typically the nonsteroid anti-inflammatory drugs (NSAIDs), also possess anti-inflammatory and analgesic properties; e.g., prostaglandin (PG)E_2, the biosynthesis of which is inhibited by NSAIDs, partly also mediates, in addition to but separately from the elevation in T_c, the proinflammatory and hyperalgesic host defense responses to infectious pathogens (Vane, and Botting, 1998a, b).

A consideration of fever in terms of its thermal element only, i.e., in accordance with its glossary definition, would thus raise the following questions: what purposes may a rise in T_c, i.e., an increase in body heat content, serve in the response to natural infections? Is it injurious or beneficial? Indeed, is it a pathological or a physiological response? Attempts to mimic the heat of fever to test its risks or benefits have been made in many studies, with ambiguous results. These have been reviewed extensively by various authors (Atkins, 1982; Banet, 1983, 1986; Blatteis, 1986; Duff, 1986; Kluger, 1979, 1986, 1991, 1997; Kluger et al., 1998; Kozak, 1993; Mackowiak, 1994, 1997a, b) and therefore will not be reviewed here again except in the context of the present evaluation of the risks or benefits of heat/fever.

2. Heat and host defense

That heat itself may be an integral part of host defense is suggested by the fact that it is a characteristic sign of cutaneous inflammatory responses. It occurs as the result of the noxious stimulus-induced local release of various vasodilatory mediators (Majno and Joris, 1996; Ward and Lentsch, 1999), thus allowing the inflow of warm blood from the core into the cooler skin. This increased blood supply not only brings neutrophils and monocytes to the afflicted site to phagocytize the invading organisms and to contribute various immune factors, but the added heat, in coordination with these latter factors (chemotaxis), also hastens their migration across venules into the tissue toward the inflamed locus

Table 3
Some characteristic acute-phase responses to infectious pathogens or their products

T_c↑		
Slow wave sleep↑		
Feeding↓		
Pituitary hormones		
ACTH↑	PRL↑	TSH↓
GH↑	LH↓	β-E↑
AVP↑	αMSH↑	SRIF↑
Plasma Fe↑, Zn↓, Cu↑		
Erythropoiesis↓		
Neutrophils↑		
Sympathetic nervous activity↑		
Acute-phase proteins		
C-reactive protein↑	Serum amyloid A↑	α_2-HS glycoprotein↓
Albumin↓	IGF-1↓	Transferrin↓
Haptoglobin↓	Fibrinogen↑	Ceruloplasmin↑
Complement↑	α_1-acid glycoprotein↑	α_1-antichymotrypsin↑
PLA_2↑	IL-1RA↑	LBP↑
Bone substance↓		
Muscle proteolysis↑		
Gluconeogenesis↓		
Lipogenesis↑		
Pancreatic insulin↑, glucagon↑		

(thermotaxis). The biological activities of these immune factors are also enhanced by heat (see later), further helping to resolve the inflammation. But is this hyperthermic response to inflammation of the skin analogous to the febrile response to infection in the core? Although an infection that develops in the core also evokes increased blood flow to the infected locus, the blood that perfuses this site is at the temperature of the core, i.e., inflamed inner organs cannot become hotter by increased inflow of blood because they are already as hot as the blood that perfuses them. Could fever then be to the body core the systemic analog of the local heat response to inflammation of the body wall? It is noteworthy in this regard that there exists in infection an upper febrile limit (“hyperthermic ceiling” [Mackowiak and Boulant, 1996]) such that the T_c does not reach a level at which T per se becomes lethal to the host.

The principal objectives of anti-infective host defense are to eradicate from the body any pathogenic microorganisms and/or their products that may have invaded it, to forestall the potentially deleterious effects of these invading agents, and to repair any damage that they may have caused. This process begins with the almost immediate activation of an extensive, nonspecific host defense response, the innate immune response. Besides the induction of multiple immune factors, the overall response consists of a panoply of both simultaneous and sequential reactions, many of them centrally mediated, termed the “acute-phase response” (Kushner and Rzewnicki, 1999; Munford and Pugin, 2001). It is manifested, in addition to fever, by the sickness behavior mentioned earlier as well as by an array of neural, endocrine, and metabolic changes (Table 3). On this basis, since the rise in T_c is a component of the characteristic acute-phase response to infectious noxa, a quick answer to the questions raised in the previous section is that fever is properly a “physiological” response. It is, consequently, homeostatic and, as such, presumptively “beneficial.” This was, in fact, the established viewpoint for a long time (see the opening quotations) until aspirin was introduced commercially in 1899 and, thanks to its apparently negligible adverse effect on the outcome of disease, became a routine antipyretic prescription (Styrt and Sugarman, 1990; Klein and Cunha, 1996; Mackowiak and Plaisance, 1998; Kaven et al., 2000; Plaisance and Mackowiak, 2000; Mackowiak, 2000a, b; Aronoff and Neilson, 2001). Then why “is fever good or bad?” still an issue? Probably because the overall evidence supporting a role for fever as enabling animals to resist infection is, in fact, confusing due to the fact that the available data are confounded by the diversity of experimental models that were used to evoke fever and/or to evaluate the outcome of the induced infection.

3. Heat and survival

Many studies have suggested that warming the body is associated with shortened disease duration and improved survival. In the best known of those studies,

Bernheim and Kluger (1976) found a direct correlation between the ability of desert iguanas to resist an usually lethal infection caused by the subdermal administration of *Aeromonas hydrophilia* and an increase in T_c achieved by these reptiles either behaviorally choosing or being placed in an appropriately warm environment. Subsequent reports that various other ectothermic vertebrates and some invertebrates can develop fever in response to different pyrogens (reviewed in Kluger, 1979, 1991, 1997) have contributed to the notion that fever is phylogenetically very ancient and therefore likely to have survival value. If fever, thus, were beneficial, then by extrapolation, suppression of fever should be detrimental. Indeed, the heat-seeking behavior of the infected lizards described above was abolished by sodium salicylate treatment, and this severely reduced their survival rates (Bernheim and Kluger, 1976). But, on the other hand, not all ectotherms respond with fever to pyrogenic stimuli (Zurovsky et al., 1987a, b).

Although several studies have also documented improved survival of febrile infected patients as compared to patients who for some reason were unable to generate fever, and other studies have reported reduced survival when various infected endotherms were pretreated with antipyretics (reviewed in Mackowiak, 1997b, 2000b), such studies are difficult to interpret because the outcome may have been dictated by the nature of the infectious pathogen, the course of the infection itself, ancillary treatments that could not be withheld for ethical reasons, the overall status of the host, and other confounding variables. Furthermore, since antipyretics are prototypical home and medically prescribed remedies of fever with, in general, no untoward effect, it may be surmised that the administration of, in particular, NSAIDs does not adversely affect resistance to infection or survival from it. Indeed, the concatenation of adaptive acute-phase responses which accompanies fever is not generally affected by these agents, although it should be noted that the blockade of PGE_2 synthesis by NSAIDs also disinhibits the production of cytokines (reviewed in Vane and Botting, 1998a, b), which may engender deleterious consequences in the host. Interpretation of the results of specifically designed human experiments have been complicated in that nonreplicating agonists, such as high doses of endotoxin or proinflammatory cytokines rather than viable infectious pathogens, were administered, usually in a single bolus. Also, in many studies, the subjects' T_cs were manipulated by external warming before or after the infectious challenge. However, no specific, controlled studies on the effect of the use of NSAIDs on the mortality and morbidity potentially associated with infectious fevers in human beings have as yet been reported, to our best knowledge. Other compensatory mechanisms that may be triggered homeostatically when fever is suppressed could also account for the absence of demonstrable differences in patients whose infections are allowed to run their courses without NSAIDs.

Hence, despite the ubiquity of the febrile response, its beneficial survival value cannot be derived with assurance from those studies. Indeed, a direct, in vivo test of its adaptive value is hard to design in homeotherms because it is difficult to isolate T_c as a single manipulated variable, and also because the morbidity and mortality associated with infectious disease are determined in large measure, as indicated earlier, by the co-operation of other host defense systems, most notably the immune system. It should also be noted in this regard that many aged animals exhibit reduced febrile responses (Bender and Scarpace, 1997; Roghmann et al., 2001) and that the neonates of most species do not generally develop fever in the first few days of life (Blatteis, 1980, 1983, 1989; Bonadio et al., 1990; McCarthy, 1997), yet all produce cytokines and acute-phase reactants (Dinarello et al., 1981; Pillay et al., 1994; Roubenoff et al., 1998; Bruunsgaard et al., 2001) and generally survive infection (McCarthy, 1997), suggesting that other factors in the host defense system can supplant fever per se for survival. Albeit that, again, no controlled studies exist that show that aged animals or neonates would fare better or worse if their T_c were elevated to febrile levels, a general evolutionary theory of fever as a survival adaptation is thus, as yet, only an interesting hypothesis.

But the fact remains that heat/fever is a part of the acute-phase response. Might heat be beneficial by virtue of a direct inhibitory effect on the pathogenicity of infectious microorganisms? And/or, since antimicrobial resistance depends in large part on an activated immune system, might the role of heat be to mediate this activation?

4. Heat and microorganisms

The notion that the heat of fever may kill invading infectious microorganisms underlied Wagner-Jauregg's rationale and earned him the Nobel Prize in Physiology or Medicine in 1927 when he successfully treated neurosyphilis by giving malaria to his patients and then curing them with quinine (Wagner-Jauregg, 1965; Whitrow, 1990). Similarly successful outcomes of "fever treatments" were subsequently reported for other pathogens (certain bacilli, fungi, parasites, and viruses) (reviewed in Kluger, 1979, 1997). It is now clear that these beneficial results were due to the fact that microorganisms that live optimally in Ts from 35°C to 37°C are intolerant to Ts above this range; i.e., Ts in the physiologic febrile range (38–41°C) inhibit their growth, denature their proteins, and destroy their infectious activity (reviewed in Rodbard et al., 1980;

Mackowiak, 1991). They thus preferentially colonize the relatively cooler anatomic regions of the body, viz., skin, distal extremities, external ears, nasal cartilage, and scrotum. Most pathogens, however, induce fevers that peak at levels below those that would kill them; indeed, T_cs lethal to invading microbes are rarely reached in natural disease. Thus, organisms whose optimal viable T range is within the physiologic T_c range (i.e., 33–41°C) are generally little affected by T_cs in the febrile range (Fig. 1). This fact may account for the mixed results of studies in which the effects of T on microbial death were examined in in vitro studies conducted under conditions in which Ts were above the physiologic febrile range and sustained for several hours. This is not the usual pattern in natural fever, which is characterized by variations in T_c of ~2°C over a few hours, a cycle that could allow microorganisms to adapt to degrees of heat that otherwise could be inhibitory. Moreover, although suggestive, in vitro experiments have to be interpreted with caution because they involve important variables other than T that may affect the results. For example, differences in the chemical composition of the medium, its pH and O_2 content, all affect the thermal susceptibility of the organisms. The phase of growth of the organisms also is important, since organisms that are dividing rapidly are less resistant to increases in T than organisms in the stationary phase; the availability of iron is also critical for the proliferation of some bacteria (Weinberg, 1978; Kluger and Rothenburg, 1979). These variables have not been consistently controlled. Also, while there is an implicit assumption that lower bacterial counts signify less severe infection, this does not, as mentioned earlier, necessarily correlate with fever height or host survival. For example, more *Streptococcus pneumoniae*-infected, febrile rabbits died than infected animals with attenuated fevers, despite no bacteremia in the former and bacteremia in the latter (Klastersky, 1971). Similarly, in a *Klebsiella pneumonia* peritonitis model, survival was improved and bacterial load reduced when T_c was maintained in the febrile range albeit that the tissue pathogen load at death was considerably lower in the warmer mice, suggesting that death occurred despite successful pathogen clearance (Jiang et al., 2000). It is probable, therefore, that host survival is associated more importantly with beneficial host–pathogen, i.e., immune, interactions rather than with a direct, toxic effect of heat on the pathogen.

5. Heat and immunity

Since anti-infective host defense mechanisms are fundamentally dependent on an activated immune system, an influence of heat/fever on immune responsiveness

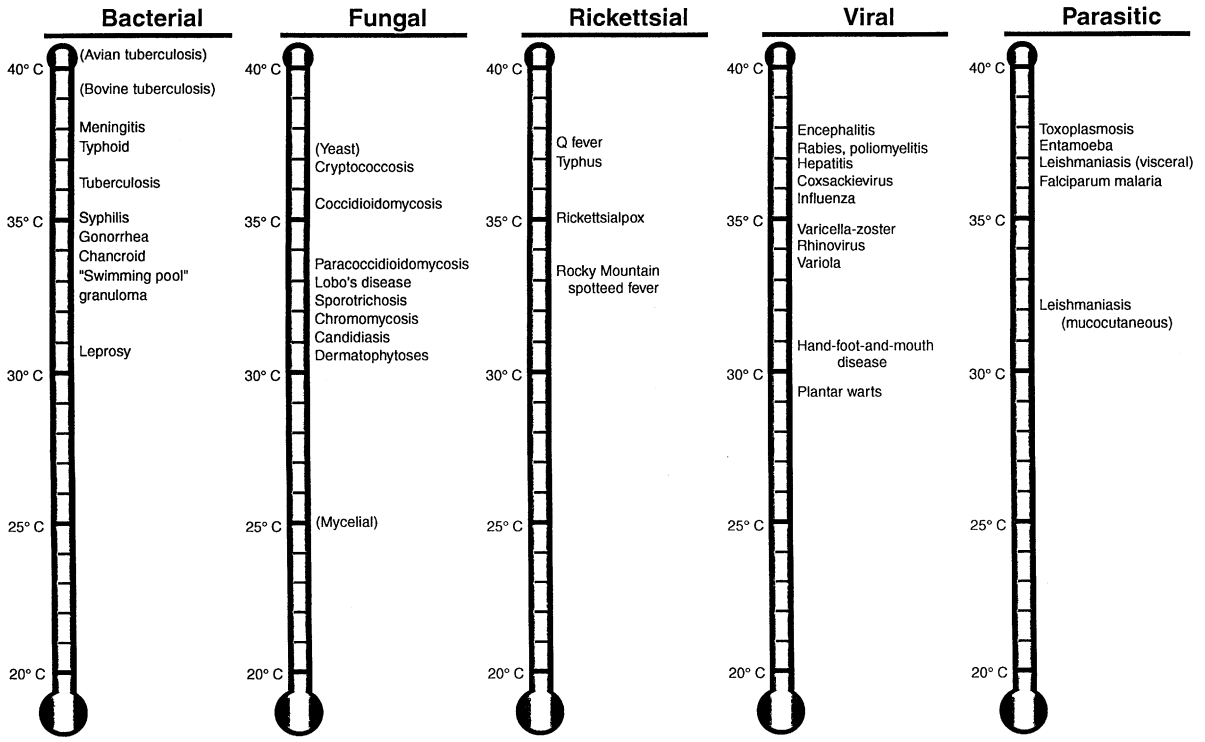

Fig. 1. Optimal viable temperature ranges of different classes of microorganisms. Adapted from Rodbard et al. (1980) and Mackowiak (1991).

might be anticipated. Indeed, thermal enhancement of various immune functions has been documented in many studies (reviewed in Roberts, 1991a, b; Hanson, 1998). Some pertinent immunological consequences of heat/fever are summarized in Table 4; among those listed, increased granulocyte emigration from the circulation toward the local site of inflammation is of interest: it was also observed in the infected lizards mentioned earlier (Bernheim et al., 1978), i.e., like heat itself, this response too is a highly conserved local defense mechanism. A priori, these effects are not surprising since some potentiation by heat of biological activities generally would be expected. However, it should be noted that, in fact, not all immune functions are potentiated by febrile range Ts. For example, the chemotactic activity of neutrophils is not enhanced and their bactericidal capacity is only weakly and inconsistently augmented, while the cytotoxic activity of natural killer cells is reduced rather than increased in the febrile range (reviewed in Hasday, 1997). These differential responses would suggest that the effects of heat/fever on immunological mechanisms may be function- and/or cell-specific, i.e., that the role of heat/fever may be more discrete in this regard that generally thought. Definitive conclusions from the available data are difficult, however, because the experimental conditions under which the various determinations were made were far from uniform. Thus, the studies were generally conducted ex vivo, using either individual or mixed cell populations from uninfected donors or donors infected with diverse pathogenic agents (e.g., various microorganims, endotoxins, or proinflammatory cytokines) administered at different times after or before cell harvesting, respectively. Moreover, different T ranges, many often exceeding the normal febrile range observed during infection, were applied for varying durations (in some cases, days) to the cells either before or after the infectious stimulus, seldom coincident with it. Consequently, although admittedly strongly suggestive, the listed effects of heat/fever on immune responsiveness are as yet only presumptively beneficial and cannot directly be linked to host survival in systemic infection.

Table 4
Some immune benefits of heat/fever

Enhanced neutrophil and monocyte motility and emigration
Enhanced phagocytosis and pinocytosis
Increased oxygen radical production by phagocytes
Increased interferon (IFN) production
Increased antiviral, antitumor, antiproliferative, and NK cell-stimulating activities of IFN
Potentiated IFN-induced anti-anaphylaxis (anergy)
Enhanced expression of F_c receptors
Increased T-helper cell activation, expression, recruitment, and cytotoxic activity
Increased antibody production
Increased T-cell proliferative response to nonspecific mitogens, IL-1 and -2, and allogeneic lymphocytes
Increased killing of intracellular bacteria
Increased bactericidal effect of antimicrobial agents
Induction of cytoprotective HSPs in host cells
Induction of pathogen HSPs, which activate host defenses

A feature of the data listed in Table 4, however, is noteworthy, viz., the majority of benefits relate to events that occur during the subsequent adaptive rather than during the initial innate immune response to infectious stimuli. This is not surprising insofar as the duration of natural fevers generally extends beyond the nonspecific into the specific stage of the immune response. Hence, it is logical to expect that its effects may impact on the immunoprotective mechanims of this latter stage as well. For example, some hours after the initial infectious challenge, circulating monocytes and activated lymphocytes (particularly type-1 T-helper cells [Th1] and B-cells) are recruited to the inflamed tissue. Repasky and her colleagues (Hughes et al., 1987; Di et al., 1997; Burd et al., 1998; Wang et al., 1998, 1999; Evans et al., 1999, 2000, 2001; Ostberg and Repasky, 2000; Ostberg et al., 2000a, b, 2001) have elegantly demonstrated how heat in the febrile range dynamically modulates the regional recruitment of circulating lymphocytes. It does so in two ways. First, one of the earliest changes that T-lymphocytes undergo during their migration toward an inflamed site is cellular polarization and uropod formation; this process involves a reorganization of the spectrin-actin based structural cytoskeleton and of its associated molecules and results in an increase of its tensile strength. These changes are enhanced by heat alone, without any other immunological stimulant; they are not seen following more severe hyperthermic protocols. Second, lymphocyte adhesion itself is initiated by L-selectin and alpha4beta7-integrin on the microvillous processes of lymphocytes. The cells first roll, then attach onto high endothelial venules (HEV) of secondary lymphoid organs (e.g., lymph nodes, spleen) and of inflamed tissue under hemodynamic conditions by adhering to beta2-integrin and LFA-1 HEV counterreceptors (Steeber et al., 1998). Febrile Ts in vitro stimulate L-selectin and alpha4beta7-integrin-dependent adhesion to HEV through the release of autocrine factors, without affecting the surface density of these molecules. The meanwhile increased tensile strength of the lymphocytes allows the L-selectin to become firmly anchored to the structural cytoskeleton and, consequently, the adherent lymphocytes better to withstand the shear conditions in the blood vessels. This bimodal, heat-dependent regulation of the lymphocyte–endothelium adhesion mechanism thus amplifies lymphocyte delivery to lymph nodes and inflamed tissues. It is detected in lymph nodes within 2–6 h after heat stimulation and 8–24 h before antigen-specific T-cells become activated

in lymph nodes during a primary immune response. By thus helping to direct the homing molecules on lymphocytes to the corresponding adhesion molecules on HEV, heat/fever contributes to focusing the adaptive immune response to infected sites and associated lymphoid tissues while preventing the emigration of lymphocytes to other, uninflamed tissues. At the infection site, macrophages that have earlier taken up antigens present them to the arriving T-cells in a form that they can recognize (antigen-presenting cells). These T-cells, in turn, release soluble mediators, including cytokines, that activate the phagocytes to destroy the pathogens they have internalized. Phagocytes also utilize antibodies released by B-cells similarly attracted to the site to allow more effective recognition of pathogens. It should be noted in this context that the T-cells are the principal producers of cytokines once an infection has become established and the adaptive immune response is initiated; these cytokines could thus account for the continued systemic fever.

But the preceding now raises a new issue: is the complementary, heat-induced enhancement of the processes listed in Table 4 the only advantage of fever? If so, this would seem to minimize the significance of heat/fever as a primary modulator of host defense and instead relegate it to a secondary, auxiliary role. Indeed, consignment to such a role, albeit important, could justify its pharmacological suppression, since this should result only in the return of affected immune functions to their normal infectious stimulus-induced rate rather than their heat-accelerated rate of activity, without fatal interruption of host defense mechanisms—as indeed would seem to be the case in most clinical situations. But why then does fever develop so early, i.e., during the innate immune response?

6. Heat and cytokines

Although the detailed mechanisms of the afferent initiation of anti-infective host responses are still incompletely understood, it is generally agreed that endogenous factors released secondarily by, primarily, mononuclear phagocytes (blood-borne neutrophils and monocytes and tissue macrophages) activated in response to the invasion of the host by infectious pathogens play major mediatory roles. The substances thus generated belong to a class of (immuno)peptides termed cytokines; by an as yet debated mechanism, they signal the body's relevant controllers in the anterior hypothalamic area (AH) of the brain to begin the acute-phase response. Other, more proximal mediators, e.g., prostaglandin (PG)E_2, norepinephrine, etc. are thought to modulate the later steps of the response in the AH (reviewed in Blatteis and Sehic, 1997; Blatteis et al., 2000).

It is generally considered that the cytokines tumor necrosis factor (TNF)α, interleukin (IL)-1β, and IL-6 are the principal mediators of the pyrogenic response to Gram-negative bacterial infections; interferon (IFN)γ is additionally released in response to viral stimuli (Netea et al., 1999; Netea et al., 2000; Dinarello and Bunn, 1997). In vitro at room temperature, the magnitude of their expression is generally directly proportional to the endotoxic dose. In addition to their direct stimulation by endotoxin, TNFα and IL-1β also induce each other and both induce IL-6; but IL-6, in turn, downregulates TNFα and IL-1β expressions (reviewed in Dinarello, 1997a, b, 1999, 2000). In vivo following a single peripheral bolus of endotoxin, these cytokines generally culminate in blood in the sequential order TNFα, IL-1β, and IL-6, are expressed concurrently for various durations, then recede to control levels in a relatively short period (Cannon et al., 1990; Jansky et al., 1995; Kozak et al., 1998). In natural infections, however, their plasma levels do not correspond continuously and directly with the febrile course.

It should be remembered, however, that cytokines are structurally and functionally diverse proteins, with complex activities beyond pyrogenesis, some overlapping and others antagonistic. It may be speculated, therefore, that their net effect is determined by the magnitude, timing, and pattern of their collective expression. It may be further speculated that, although they are necessary for optimal host defense, their inopportune production could provoke pathogenic consequences. Indeed, their dysregulated expression often causes progressive, lethal inflammatory responses to stimuli that are not normally lethal. For example, although TNFα is an early and essential activator of host defenses and failure to express it results in persistent and potentially lethal systemic inflammation (Beutler, 1999; Marino et al., 1997), its inappropriate, high, or prolonged expression, especially in the concomitant presence of IL-1β or IFNγ, can lead to tissue injury, multiorgan failure, septic shock and death (Tracey and Cerami, 1994). It follows from the preceding that counter-regulatory mechanisms that limit the further expression of, in this example, TNFα would be vitally important. Such compensatory mechanisms, of course, exist. They include various endogenous soluble inhibitors induced by TNFα, viz., IL-4, -6, -10, -13, PGE_2, glucocorticoids, and TGF-β (Dinarello, 1997a, b), but also an endogenous physical factor, viz., increased T_c.

As would be expected, the expression and bioactivity of pyrogenic cytokines are importantly influenced by heat/fever, but the reported effects have been variable, mostly for the same reasons as those cited earlier for the inconsistency of its effects on immunity, viz., that the experimental models and designs used were very dissimilar. For example, exposure to febrile range heat

per se did not induce increases in systemic cytokine levels in BALB/C and C57 mice, but when external heat was applied immediately after an intraperitoneal injection of endotoxin, TNFα and IL-6 levels were greater in BALB/C, C57, and CD-1 mice than after endotoxin alone (Jiang et al., 1999a, b). By contrast, in vitro heat treatment of endotoxin-stimulated peritoneal macrophages resulted in decreased cytokine production as compared with controls, whereas exposure to Ts above the febrile range enhanced their release (Ensor et al., 1994; Jiang et al., 1999a, b). It now emerges that the direct effects of elevated T_c on cytokine generation may depend, in fact, on the cytokine studied, its cellular source, the magnitude of the T_c increase, and the nature of the stimulus used to induce its production. In a novel approach, Hasday and his colleagues (Hasday, 1997; Jiang et al., 2000; Singh et al., 2000; Hasday et al., 2000, 2001) have recently shown that the temporal relationship between host cell stimulation and the increase in T_c is very important. Thus, exposure of human and murine macrophages in vitro or of anesthetized mice stimulated with endotoxin and raised to T_c 39.5–40.0°C significantly shortened the duration of TNFα and IL-1β transcriptional activation. Repression of transcription was accomplished by heat shock factor (HSF)1 binding to their promoters; HSF1 is activated in macrophages by febrile range Ts as well as by, e.g., the soluble counterregulatory compounds IL-6 and PGE_2 (Singh et al., 2002). Specifically, using a murine endotoxin-challenged model of sepsis, these workers demonstrated that raising T_c to the febrile range immediately before or coincident with the endotoxic challenge reduced the rate of early TNFα production by Kupffer cells, thus leading to a self-limiting pulse of TNFα in the febrile animals; i.e., heat/fever enhanced the early expression of TNFα but, by reducing the duration of its expression, it also limited its potential toxicity. Heat/fever furthermore delayed the generation of IL-1β by these cells but enhanced that of IL-6—which, as already mentioned, downregulates TNFα and IL-1β expressions—thus preventing the simultaneous expression of both these latter cytokines and thereby avoiding their potential, synergistic, harmful effects. In further studies, this group substantiated the role of fever as a putative endogenous regulator of cytokine production by confirming in different models of inflammation that the peak levels of TNFα occur earlier and are higher in plasma and liver while, simultaneously, the early peaks of IL-1β are attenuated and its late peaks are delayed in plasma and lung and while the levels of circulating and tissue-associated IL-6 are also rising (Fig. 2). But, on the other hand, in a model of peritoneal infection, the peaks of TNFα and IFNγ were coincident, thereby enhancing local antimicrobial defenses at the primary site of infection. Taken together, these results indicate that the effects of fever are critical, complex, and specific for each cytokine

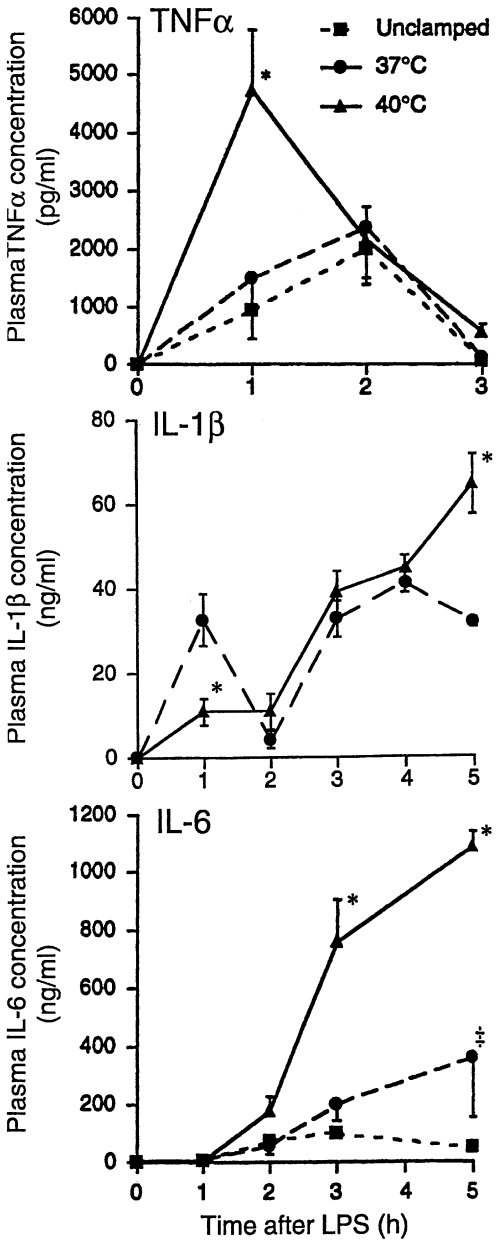

Fig. 2. Effects of endotoxin (*E. coli* lipopolysaccharide, LPS; 50 μg, ip) on the plasma levels of tumor necrosis factor (TNF)α, interleukin (IL)-1β, and IL-6, measured by ELISA, of anesthetized CD-1 mice (25–30 g; n= 6/treatment), clamped at 37°C or 40°C by suspension in constant-temperature water baths beginning 5–10 min before LPS administration. Conscious mice maintained at T_a 22–24°C were the controls (unclamped). Blood samples were collected at the times indicated. *Significantly different from corresponding unclamped mice; †significantly different from both 37°C clamped and unclamped mice. Modified from Jiang et al. (1999b).

and also for each body compartment. Thus, subtle changes in the features of the various, individual factors involved may impact profoundly on the course and resolution of the inflammatory process.

7. General conclusions

Fever, the body's most manifest sign of infectious illness, is only one of a concatenation of complex, nonspecific host defense responses to infections. Although a direct link between fever and host survival is tenuous, there is little doubt that fever is a physiological response to invasion by infectious pathogens and that, as such, it is not per se injurious to the afflicted host. But assessing the benefits of fever in vivo is complicated by the difficulty of separating the effects that are due to the thermal element of fever alone from the multivariate other physiological, neurological, biochemical, and immunological events that co-occur during the febrile response because many of these events share the same mediators. Indeed, as discussed, raising T_c, although it reduced bacterial proliferation in some instances, particularly when associated with iron deprivation, tended to reduce rather than to improve host survival. Death, when it occurred in febrile animals, was caused by collateral damage from host defenses while death in afebrile animals came as a result of overwhelming bacterial infection. Heat/fever, however, is clearly beneficial as an adjuvant to immunological functions, enhancing, e.g., the homing potential of T-lymphocytes by modulating critical steps in the signal transduction pathway involved in their polarization, activation, motility, and finally L-selectin-mediated adhesion to HEV. But more importantly, since effective antimicrobial host defense mechanisms clearly depend on the concerted interplay of many, precisely timed and patterned factors mediated by a delicate and complicated cytokine balance, fever, it would appear, creates the optimal thermal environment for their properly coordinated and appropriate expression. This evolutionarily conserved response to infection, therefore, would seem to serve a pivotal role during, particularly, the early phases of anti-inflammatory host defense responses. Hence, it would seem to this reviewer that antipyretic medications, by defeating the purpose of this precisely orchestrated and optimized host response, should be avoided and that, unless overriding conditions exist (Cooper, 1995; Klein and Cunha, 1996; Mackowiak and Plaisance, 1998; Hasday and Garrison, 2000), letting fever take its natural course would be the more salutary approach, at least early on during an infection's course. Therapeutic interventions instituted later on may interfere less with overall host defenses. But, as a matter of principle, the temporal relationship between the expressions of the various pro- and anti-inflammatory mediators and modulators induced in response to the infection (cytokines, eicosanoids, various peptides, glucocorticoids, etc.) and the timing of specific treatments (antipyretic, anti-inflammatory, analgesic, etc.) should be an important consideration in instituting such treatments.

Acknowledgements

This project was supported, in part, by NIH grants NS 34857 and NS 38594. I thank Ms. Easter Jenkins for her excellent secretarial support.

References

Aronoff, D., Neilson, E., 2001. Antipyretics: mechanisms of action and clinical use in fever suppression. Am. J. Med. 111, 304–315.

Atkins, E., 1982. Fever: it's history, cause and function. Yale J. Biol. Med. 55, 283–289.

Atkins, E., Bodel, P., 1979. Clinical fever: its history, manifestations and pathogenesis. Fed. Proc. 38, 57–63.

Banet, M., 1983. The biological function of fever: an alternative view. Funk. J. Biol. Med. 2, 211–218.

Banet, M., 1986. Fever in mammals: is it beneficial? Yale J. Biol. Med. 59, 117–124.

Barton, D., Schmitt, M.D., 1980. Fever phobia: misconceptions of parents about fevers. Am. J. Dis. Child. 134, 176–181.

Bender, B.S., Scarpace, P.J., 1997. Fever in the elderly. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 363–373.

Bernheim, H.A., Kluger, M.J., 1976. Fever: effect of drug-induced antipyresis on survival. Science 193, 237–239.

Bernheim, H.A., Bodel, P.T., Askenase, P.W., Atkins, E., 1978. Effects of fever on host defense mechanisms after infection in the lizard *Dipsosaurus dorsalis*. Br. J. Exp. Pathol. 59, 76–84.

Beutler, B., 1999. The role of tumor necrosis factor in health and disease. J. Rheumatol. 26 (Suppl. 57), 16–21.

Blatteis, C.M., 1980. In: Lipton, J.M. (Ed.), Ontogenetic Development of Fever Mechanism. Raven, New York, pp. 177–188.

Blatteis, C.M., 1983. Research in perinatal thermoregulation: recent advances. J. Therm. Biol. 8, 191–194.

Blatteis, C.M., 1986. Fever: is it beneficial? Yale J. Biol. Med. 59, 107–116.

Blatteis, C.M., 1989. Thermal homeostasis during the neonatal period. Prog. Biometeorol. 7, 35–40.

Blatteis, C.M., Sehic, E., 1997. Prostaglandin E_2: a putative fever mediator. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Raven-Lippincott, New York, pp. 117–148.

Blatteis, C.M., Sehic, E., Li, S., 2000. Pyrogenic sensing and signaling: old views and new concepts. Clin. Infect. Dis. 31 (Suppl. 5), S168–S177.

Blumenthal, I., 1998. What parents think of fever. Fam. Pract. 15, 513–518.

Bonadio, W.A., Romine, K., Gyuro, J., 1990. Relationship of fever magnitude to rate of serious bacterial infections in neonates. J. Pediatr. 116, 733–735.

Bruunsgaard, H., Pedersen, M., Pedersen, B.K., 2001. Aging and proinflammatory cytokines. Curr. Opin. Hematol. 8, 131–136.

Burd, R., Dziedzic, T.S., Xu, Y., Caligiuri, M.A., Subjeck, J.R., Repasky, E.A., 1998. Tumor cell apoptosis, lymphocyte recruitment and tumor vascular changes are induced by low temperature, long duration (fever-like) whole body hyperthermia. J. Cell Physiol. 177, 137–147.

Cannon, J.G., 2000. Inflammatory cytokines in nonpathological states. News Physiol. Sci. 15, 298–303.

Cannon, J.G., Tompkins, R.G., Gelfand, J.A., Michie, H.R., Stanford, G.G., van der Meer, J.W., Endres, S., 1990. Circulating interleukin-1 and tumor necrosis factor in septic shock and experimental endotoxin fever. J. Infect. Dis. 161, 79–84.

Cooper, K.E., 1995. Fever and Antipyresis. Cambridge University Press, Cambridge, UK, 182 p.

Crocetti, M., Maghbeli, N., Serwint, J., 2001. Fever phobia revisited: have parental misconceptions about fever changed in 20 years? Pediatrics 107, 1241–1246.

Di, Y.-P., Repasky, E.A., Subjeck, J.R., 1997. Distribution of HSP70, protein kinase C, and spectrin is altered in lymphocytes during a fever-like hyperthermia exposure. J. Cell Physiol. 172, 44–54.

Dinarello, C.A., 1996. Biologic basis for interleukin-1 in disease. Blood 87, 2095–2147.

Dinarello, C.A., 1997a. Cytokines as endogenous pyrogens. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 87–116.

Dinarello, C.A., 1997b. Role of pro- and anti-inflammatory cytokines during inflammation: experimental and clinical findings. J. Biol. Regul. Homeost. Agents 11, 91–103.

Dinarello, C.A., 1999. Cytokines as endogenous pyrogens. J. Infect. Dis. 179 (Suppl. 2), S294–S304.

Dinarello, C.A., 2000. Proinflammatory cytokines. Chest 41, 503–508.

Dinarello, C.A., Bunn, P.A., 1997. Fever. Semin. Oncol. 24, 288–298.

Dinarello, C.A., Pomerantz, B.J., 2001. Proinflammatory cytokines in heart disease. Blood Purif. 19, 314–321.

Dinarello, C.A., Shparber, M., Kent, E.F., Wolff, S.M., 1981. Production of leukocytic pyrogen from phagocytes of neonates. J. Infect. Dis. 144, 337–343.

Duff, G., 1986. Is fever beneficial to the host: a clinical perspective. Yale J. Biol. Med. 59, 125–130.

Ensor, J.E., Wiener, S.M., McCrea, K.A., Viscardi, R.M., Crawford, E.K., Hasday, J.D., 1994. Differential effects of hyperthermia on macrophage interleukin-6 and tumor necrosis factor-α expression. Am. J. Physiol. 266, C967–C974.

Evans, S.S., Schleider, D.M., Bowman, L., Francis, M.L., Kansas, G.S., Black, J.D., 1999. Dynamic association of L-selectin with the lymphocyte cytoskeletal matrix. J. Immunol. 162, 3615–3624.

Evans, S.S., Bain, M.D., Wang, W.-C., 2000. Fever range hyperthermia stimulates a4b7 integrin-dependent lymphocyte–endothelial adhesion. Int. J. Hyperthermia 16, 45–59.

Evans, S.S., Wang, W.-C., Bain, M.D., Burd, R., Ostberg, J.R., Repasky, E.A., 2001. Fever-range hyperthermia dynamically regulates lymphocyte delivery to high endothelial venules. Blood 97, 2727–2733.

Hanson, D.F., 1998. Fever, temperature, and the immune response. Ann. NY Acad. Sci. 813, 453–464.

Hasday, J.D., 1997. The influence of temperature on host defenses. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 177–196.

Hasday, J.D., Garrison, A., 2000. Antipyretic therapy in patients with sepsis. Clin. Infect. Dis. 31, S234–S241.

Hasday, J.D., Bannerman, D., Sakarya, S., Cross, A.S., Singh, I.S., Howard, D., Drysdale, B.-E., Goldblum, S.E., 2001. Exposure to febrile temperature modifies endothelial cell response to tumor necrosis factor-α. J. Appl. Physiol. 90, 90–98.

Holtzclaw, B., 1995. The febrile response in critical care: state of the science. Heart Lung 21, 482–501.

Hughes, C.S., Repasky, E.A., Bankert, R.B., Johnson, R.J., Subjeck, J.R., 1987. Effects of hyperthermia on spectrin expression patterns of murine lymphocytes. Radiat. Res. 112, 116–123.

Iriki, M., 1988. Fever and fever syndrome—current problems. Jpn. J. Physiol. 38, 233–250.

IUPS Thermal Physiology Commission, 2001. Glossary of terms for thermal physiology. Jpn. J. Physiol. 51, 245–280.

Jansky, L.S., Vybiral, S., Pospisilova, D., Roth, J., Dorand, J., Zeisberger, E., Kaminkova, J., 1995. Production of systemic and hypothalamic cytokines during the early phase of endotoxin fever. Neuroendocrinology 62, 55–61.

Jiang, Q., DeTolla, L., van Rooijen, N., Singh, I.S., Fizgerald, B., Lipsky, M.M., Kane, A.S., Cross, A.S., Hasday, J.D., 1999a. Febrile-range temperature modifies early systemic tumor necrosis factor alpha expression in mice challenged with bacterial endotoxin. Infect. Immun. 67, 1539–1546.

Jiang, Q., DeTolla, L., Singh, I.S., Gatdula, L., Fitzgerald, B., van Rooijen, N., Cross, A.S., Hasday, J.D., 1999b. Exposure to febrile temperature upregulates expression of pyrogenic cytokines in endotoxin-challenged mice. Am. J. Physiol. 276, R1653–R1660.

Jiang, Q., Cross, A.S., Singh, I.S., Chen, T.T., Viscardi, R.M., Hasday, J.D., 2000. Febrile core temperature is essential for optimal host defense in bacterial peritonitis. Infect. Immun. 68, 1265–1270.

Kaven, I., Plaisance, M.D., Mackowiak, P.A., 2000. Antipyretic therapy. Arch. Intern. Med. 160, 449–456.

Klastersky, J., 1971. Etude experimentale et clinique des effets favorables et défavorables de la fiévre et de l' administration de corticoides au cours d' infections bactériennes. Acta Clin. Belg. 26 (Suppl. 6), 1–84.

Klein, N., Cunha, B., 1996. Treatment of fever. Infect. Dis. Clin. Amer. 10, 211–216.

Kluger, M.J., 1979. Fever. Its Biology, Evolution and Function. Princeton University Press, Princeton, NJ, 195p.

Kluger, M.J., 1986. Is fever beneficial. Yale J. Biol. Med. 59, 89–95.

Kluger, M.J., 1991. The adaptive value of fever. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management. Raven Press, New York, pp. 105–124.

Kluger, M.J., 1997. The adaptive value of fever. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 255–266.

Kluger, M.J., Rothenburg, B.A., 1979. Fever and reduced iron: their interaction as a host defense response to bacterial infection. Science 203, 374–376.

Kluger, M.J., Kozak, W., Conn, C.A., Leon, L.R., Soszynski, D., 1998. Role of fever in disease. Ann. NY Acad. Sci. 806, 224–233.

Kozak, W., 1993. Fever: a possible strategy for membrane homeostasis during infection. Perspect. Biol. Med. 37, 14–34.

Kozak, W., Kluger, M.J., Soszynski, D., Conn, C.A., Rudolph, K., Leon, L.R., Zheng, H., 1998. IL-6 and IL-1β in fever. Ann. NY Acad. Sci. 856, 33–49.

Kramer, M.S., Niamark, L., Leduc, D.G., 1985. Parental fever phobia and its correlates. Pediatrics 70, 1110–1113.

Kushner, I., Rzewnicki, D., 1999. Acute phase response. In: Gatlin, J.I., Snyderman, R. (Eds.), Inflammation: Basic Principles and Clinical Correlates, 3rd Edition. Lippincott Williams and Wilkins, Philadelphia, PA, pp. 317–329.

Mackowiak, P.A., 1991. Direct effects of physiologic variations in temperature on pathogenic microorganisms. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management. Raven Press, New York, pp. 167–182.

Mackowiak, P.A., 1994. Fever: blessing or curse? A unifying hypothesis. Ann. Intern. Med. 120, 1037–1040.

Mackowiak, P.A. (Ed.), 1997a. Fever: Basic Mechanism and Management, 2nd Edition, Lippincott-Raven, Philadelphia, 506p.

Mackowiak, P.A., 1997b. Benefit versus risks of the febrile response. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 279–286.

Mackowiak, P., 2000a. Physiological rationale for suppression of fever. Clin. Infect. Dis. 31 (Suppl 5), S185–S189.

Mackowiak, P.A., 2000b. Diagnostic implications and clinical consequences of antipyretic therapy. Clin. Infect. Dis. 31 (Suppl 5), S230–S233.

Mackowiak, P.A., Boulant, J., 1996. Fever's glass ceiling. Clin. Infect. Dis. 22, 525–536.

Mackowiak, P.A., Plaisance, K., 1998. Benefits and risks of antipyretic therapy. Ann. NY Acad. Sci. 856, 214–223.

Majno, G., Joris, I., 1996. Cells, tissues, and disease. Principles of general pathology. The Four Cardinal Signs of Inflammation, Blackwell Science, Cambridge, MA, pp. 365–383 (Chapter 10).

Marino, M.W., Dunn, A., Grail, D., Inglese, M., Noguchi, Y., Richards, E., Jungbluth, A., Wada, H., Moore, M., Williamson, B., Basu, S., Old, I., 1997. Characterization of tumor necrosis factor-deficient mice. Proc. Natl. Acad. Sci. USA 94, 8093–8098.

McCarthy, P.L., 1997. Fever in infants and children. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management, 2nd Edition. Lippincott-Raven, Philadelphia, pp. 351–362.

Munford, R.S., Pugin, J., 2001. The crucial role of systemic responses in the innate (non-adaptive) host defense. J. Endotoxin Res. 7, 327–332.

Netea, M.G., Kullberg, B.J., van der Meer, J.W., 1999. Do only circulating pyrogenic cytokines act as mediators in the febrile response? A hypothesis. Eur. J. Clin. Invest. 29, 351–356.

Netea, M.G., Kullberg, B.J., van der Meer, J.W., 2000. Circulating cytokines as mediators of fever. Clin. Infect. Dis. 31 (Suppl. 5), S178–S184.

Ostberg, R.R., Repasky, E.A., 2000. Comparison of the effects of two different whole body hyperthermia protocols on the distribution of murine leukocyte population. Int. J. Hyperthermia 16, 29–43.

Ostberg, J.R., Patel, R., Repasky, E.A., 2000a. Regulation of immune activity by mild (fever-range) whole body hyperthermia: effects on epidermal Langerhans cells. Cell Stress Chaperones 5, 458–461.

Ostberg, J.R., Taylor, S.L., Baumann, H., Repasky, E.A., 2000b. Regulatory effects of fever-range whole-body hyperthermia on the LPS-induced acute inflammatory response. J. Leukoc. Biol. 68, 815–820.

Ostberg, J.R., Gellin, C., Patel, R., Repasky, E.A., 2001. Regulatory potential of fever-range whole body hyperthermia on Langerhans cells and lymphocytes in an antigen-dependent cellular immune response. J. Immunol. 167, 2666–2670.

Pillay, V., Savage, N., Laburn, H., 1994. Circulating cytokine concentrations and cytokine production by monocytes from newborn babies and adults. Pflügers Arch. 428, 197–201.

Plaisance, K.I., Mackowiak, P.A., 2000. Antipyretic therapy: physiologic rationale, diagnostic implications, and clinical consequences. Arch. Intern. Med. 160, 449–456.

Roberts Jr., N.J., 1991a. Impact of temperature elevation on immunologic defenses. Rev. Infect. Dis. 13, 462–472.

Roberts Jr., N.J., 1991b. Immunological consequences of fever. In: Mackowiak, P.A. (Ed.), Fever: Basic Mechanisms and Management. Raven Press, New York, pp. 243–251.

Rodbard, D., Wachslicht-Rodbard, H., Rodbard, S., 1980. Temperature: a critical factor determining localization and natural history of infectious, metabolic and immunological diseases. Perspect. Biol. Med. 23, 439–474.

Roghmann, M.C., Warner, J., Mackowiak, P.A., 2001. The relationship between age and fever magnitude. Am. J. Med. Sci. 322, 68–70.

Roubenoff, R., Harris, T.B., Abad, L.W., Wilson, P.W., Dallal, G.E., Dinarello, C.A., 1998. Monocyte cytokine production in an elderly population: effect of age and inflammation. J. Gerontol. A Biol. Sci. Med. Sci. 53, M20–M26.

Singh, I.S., Viscardi, R.M., Kalvakolanu, I., Calderwood, S., Hasday, J.D., 2000. Inhibition of tumor necrosis factor-α transcription in macrophages exposed to febrile range temperature. J. Biol. Chem. 275, 9841–9848.

Singh, I.S., He, J.-R., Calderwood, S., Hasday, J.D., 2002. A high-affinity HSF-1 binding site in the 5′-untranslated region of the murine tumor necrosis factor-α gene is a transcriptional repressor. J. Biol. Chem. 277, 4981–4988.

Sirvent, J.-L., 2001. Prognostic value of cytokines in SIRS general medical patients. Cytokine 15, 232–236.

Steeber, D.A., Tang, M.L., Zhang, X.Q., Muller, W., Wagner, N., Tedder, T.F., 1998. Efficient lymphocyte migration

across high endothelial venules of mouse Peyer's patches requires overlapping expression of L-selectin and b7 integrin. J. Immunol. 161, 6638–6647.

Styrt, B., Sugarman, B., 1990. Antipyresis and fever. Arch. Intern. Med. 150, 1589–1597.

Tracey, K., Cerami, A., 1994. Tumor necrosis factor: a pleiotropic cytokine and therapeutic target. Ann. Rev. Med. 45, 491–503.

Vane, J.R., Botting, R.M., 1998a. Mechanism of action of nonsteroidal antiinflammatory drugs. Am. J. Med. 104, 2S–8S; discussion 21S–22S.

Vane, J.R., Botting, R.M., 1998b. Antiinflammatory drugs and their mechanisms of action. Inflamm. Res. 47 (Suppl. 2), S78–S87.

Wagner-Jauregg, J., 1965. The treatment of dementia paralytica by malaria inoculation. In: Nobel Lectures: Physiology or Medicine, 1922–1941. Elsevier, New York, pp. 159–160.

Wang, W.-C., Goldman, L.M., Schleider, D.M., Appenheimer, M.M., Subjeck, J.R., Repasky, E.A., Evans, S.S., 1998. Fever-range hyperthermia enhances L-selectin-dependent adhesion of lymphocytes to vascular endothelium. J. Immunol. 160, 961–969.

Wang, X.-Y., Ostberg, J.R., Repasky, E.A., 1999. Effect of fever-like whole body hyperthermia on lymphocyte spectrin distribution, protein kinase C activity, and uropod formation. J. Immunol. 162, 3378–3387.

Ward, P.A., Lentsch, A.B., 1999. The acute inflammatory response and its regulation. Arch. Surg. 134, 666–669.

Weinberg, E.D., 1978. Iron and infection. Microbiol. Rev. 42, 45–66.

Whitrow, M., 1990. Wagner-Jauregg and fever therapy. Med. Hist. 34, 294–310.

Zitelli, B.J., 1991. Fever phobia and the adaptive value of fever. Indian J. Pediatr. 58, 275–278.

Zurovsky, Y., Mitchell, D., Laburn, H., 1987a. Pyrogens fail to produce fever in the leopard tortoise *Geochelone pardalis*. Comp. Biochem. Physiol. A 87, 467–469.

Zurovsky, Y., Brian, T., Laburn, H., Mitchell, D., 1987b. Pyrogens fail to produce fever in the snakes *Psammophis phillipsii* and *Lamprophis fugilinosus*. Comp. Biochem. Physiol. A 87, 911–914.