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Concepts of Fever: Recent Advances and Lingering Dogma

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Fever has been a preoccupation of clinicians since medicine's beginning. One might therefore expect that basic concepts relating to this physiological response would be well delineated and that such concepts would be widely known. In fact, only in the past several decades has the febrile response been subjected to scientific scrutiny. As a result of recent scientific investigation, modern concepts have evolved from a perception of fever as nothing more than a rise in core temperature to one in which fever is recognized as a complex physiological response characterized by a cytokine-mediated rise in temperature, as well as by generation of acute-phase reactants and activation of a panoply of physiological, endocrinologic, and immunologic systems. The average clinician appears to have little more than a regrettably rudimentary knowledge of these modern concepts of fever. This symposium summary considers many such concepts that have immediate relevance to the practice of medicine.

Introduction—*Philip A. Mackowiak, M.D.*

Although fever is recognized clinically by its thermal characteristics, it is in fact a complex physiological response to disease, characterized by a cytokine-mediated rise in core temperature, generation of acute-phase reactants, and activation of numerous physiological, endocrinologic, and immunologic systems. The limited data available (*vide infra*) suggest that the average physician has at best a rudimentary knowledge of the response.

The symposium summarized here considered the current status of scientifically derived knowledge of the febrile response. This symposium, which was held in Baltimore in June 1995, brought together a cadre of scientists/clinicians working in the field. It was designed to address concepts especially pertinent to clinical practice and to identify areas in which such concepts are likely to lead to significant advances in patient care in the near future.

The symposium began with a discussion of the thermal properties of the human body and then examined a question that has dogged clinicians since the earliest days of the profession: the diagnostic and prognostic significance of the fever pattern. It also considered the physiological mediators and metabolic products of the febrile response and how these might be manipulated to benefit patients afflicted with a variety of disorders. Finally, fever in HIV-infected patients—"the new frontier"—was examined as a prototypic clinical situation in which immediate opportunities exist for direct clinical application of evolving basic concepts of the febrile response.

Thermal Properties of the Human Body—*Philip A. Mackowiak, M.D.*

Fever has been the subject of intense scrutiny since the earliest days of clinical medicine. Therefore, one might reasonably expect that basic concepts pertaining to the febrile response would have long since been elucidated and that such concepts would be firmly entrenched in the thinking of modern-day clinicians. In fact, after over a millennium of clinical investigation, there is not even a generally accepted definition of fever. The enormity of our burden of ignorance in this regard is exemplified by the 1990 edition of *Steadman's Medical Dictionary* [1], which defines fever simply as "a bodily temperature above the normal of 98.6°F (37°C)"!

If one limits assessment of the medical profession's knowledge of the febrile response to its thermal properties, it is clear that even with regard to this isolated feature of the response, most physicians have, at best, an inchoate concept of fever. In a recently published survey [2], 75% of the 270 responding physicians and physicians-in-training offered 37°C (98.6°F) as

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their definition of "normal body temperature" (table 1). Only 4% specified a particular body site (e.g., oral or rectal) for temperature measurements referred to in their definition.

Temperatures selected to define fever (i.e., the lower end of the febrile range) varied between 36.9°C (98.5°F) and 40°C (104°F). Although 73% of those surveyed expressed a belief in the existence of a limit to the height of temperatures attained during fever, there was not a consensus as to the specific temperature defining the upper limit of the febrile range. Finally, infectious disease consultants surveyed did not appear to be more knowledgeable of these concepts than generalists or other specialists.

The origin of these perceptions of body temperature is uncertain, but in all likelihood it lies among the writings of Carl Wunderlich, who in 1868 published a book on clinical thermometry that many regard, to this day, as the definitive work on the subject [3]. Unfortunately, several of Wunderlich's dictums concerning body temperature, like the perceptions of modern-day physicians, appear to be in error [4, 5].

According to Wunderlich, "when the organism (man) is in a normal condition, the general temperature of the body maintains itself at the physiologic point: 37°C = 98.6°F" [6]. Although several investigations since Wunderlich's have recorded mean temperatures of normal adult populations closer to 36.6°C (98.0°F) [7], Wunderlich's intimation that 37°C (98.6°F) is the most normal of temperatures persists to this day, not only in lay thinking but in medical writing as well [8–12].

In 1992 investigators at the University of Maryland published a descriptive analysis of 700 baseline oral temperature observations for 148 healthy men and women, aged 18–40 years [4]. In this population, oral temperatures exhibited a range of 35.6°C (96.0°F) to 38.2°C (100.8°F), an overall mean of 36.8 ± 0.4°C (98.2 ± 0.7°F), median of 36.8°C (98.2°F), and mode of 36.7°C (98.0°F); 37°C (98.6°F) accounted for only 56 (8%) of the 700 oral temperature observations recorded (figure 1).

Thus, these data suggest that 37°C (98.6°F) has no special significance vis á vis body temperature of healthy young adults, when such temperature is measured orally with modern thermometers. In the University of Maryland study population,

37°C (98.6°F) was not the overall mean temperature, the mean temperature of any of the time periods studied, the median temperature, or the single most frequently recorded temperature. Furthermore, it did not fall within the 99.9% confidence intervals for the sample mean (36.7–36.8°C; 98.1–98.2°F).

Wunderlich regarded 38.0°C (100.4°F) as the upper limit of normal body temperature and, by extrapolation, any temperature greater than 38.0°C (100.4°F) as fever [6]. Modern medical textbooks differ in their definition of the upper limit of normal oral temperature. Published values include 37.1°C (98.8°F) and 38°C (100.4°F) in textbooks of physiology [13, 14], 37.2°C (99.0°F) in *Harrison's Principles of Internal Medicine* [15], and 37.4°C (99.4°F) in a recently published monograph on fever [16]. As noted above, a widely used medical dictionary defines this same upper limit as 37°C (98.6°F) [1].

The source of the confusion over what constitutes the upper limit of normal body temperature, I believe, is individual variability, which limits the application of mean values derived from population studies to individual subjects, and the fact that the maximum oral temperature (like the mean temperature) in a population varies according to time of day and the site at which temperature measurements are taken.

In the University of Maryland study population, 37.2°C (98.9°F) was the maximum oral temperature (i.e., the 99th percentile) recorded at 6:00 A.M., whereas at 4:00 P.M. the maximum oral temperature observed reached 37.8°C (99.9°F) (figure 2) [4]. Thus, these data suggest that when modern thermometers are used to monitor oral temperature in young or middle-aged adults, fever is most appropriately defined as an early morning temperature of ≥37.2°C (≥99.0°F) or a temperature of ≥37.8°C (≥100°F) at anytime during the day.

Wunderlich wrote that "[temperature] oscillates even in healthy persons according to time of day by 0.5°C = 0.9°F" [6] and that "the lowest point is reached in the morning hours between two and eight, and the highest in the afternoon between four and nine" [17]. Modern authorities have generally concurred with Wunderlich's observations on such matters [10, 15]. However, Täuber [11] has recently suggested that the amplitude of diurnal variation might be as high as 1°C (1.8°F). The University of Maryland data are more consistent with Wunderlich's

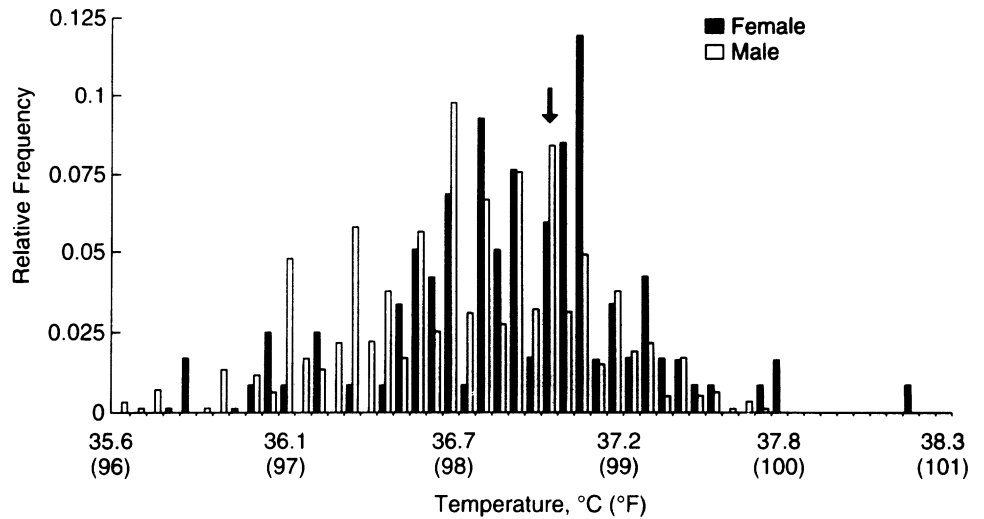
Table 1. Definitions of "normal temperature" given in a recent survey [2], according to medical specialty.

Medical specialty*	Percentage of respondents subscribing to indicated definition		
	37°C (98.6°F)	37°C, ± (98.6°F, ±)	Other
Generalists (75)	66.7	20.0	13.3
Infectious disease subspecialists (20)	60.0	20.0	20.0
Other subspecialists (50)	62.0	18.0	20.0
Students (125) [†]	88.0	5.6	6.4
All groups (270)	75.0	13.0	12.0

* In parentheses is the no. of subjects answering the question.

[†] Data are significantly different from those for graduate physicians ($P < .001$).

Figure 1. Frequency distribution of 700 baseline oral temperatures obtained during 2 consecutive days of observation of 148 healthy young volunteers [4]. Arrow indicates location of 98.6°F (37°C). (Reprinted from [4] with permission.)



view (figure 2) [4]. Nevertheless, University of Maryland subjects exhibited considerable individual variability; some had daily temperature oscillations as wide as 1.3°C (2.4°F), and others' oscillations were as narrow as 0.1°C (0.1°F).

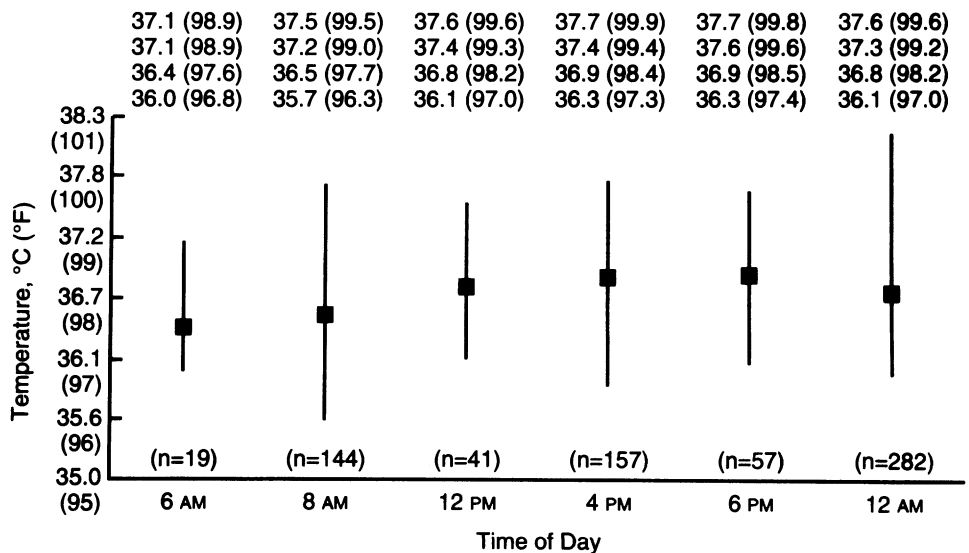
According to Wunderlich, women have slightly higher normal temperatures than men and often have greater and more sudden changes in temperature [6]. In a study of 9 healthy young adults (6 male and 3 female), Dinarello and Wolff [18] corroborated both observations. In the University of Maryland survey, women had a slightly higher average oral temperature than men (36.9°C [98.4°F] vs. 36.7°C [98.1°F]; Student's *t*-test: $P < .001$, $DF = 698$), but they did not exhibit greater average diurnal temperature oscillations than those of their male counterparts (0.56°C [1.00°F] vs. 0.54°C [0.97°F]).

Wunderlich did not personally study the influence of race on body temperature. Instead, he deferred to the observation

of "Livingstone, Travels in South Africa, p 509 [showing] temperatures of natives 1.8°C = 2°F [sic] greater than his own" [6]. In the University of Maryland survey, there was a trend toward higher temperatures among black subjects than white subjects, with the differences approaching but not quite reaching statistical significance (Student's *t*-test: $P = .06$; general linear model: $P = .05$).

It has been maintained for over a century that the elderly have lower body temperatures than do younger persons [6]. In a study reported in the *Lancet* in 1948, Howell [19] seemed to validate this belief. Although there are considerable data suggesting that thermoregulation is impaired in the elderly because of various effects of aging on the autonomic system [20], recent investigations have not shown lower average core temperatures among healthy elderly persons than among young healthy people [21].

Figure 2. Mean oral temperatures (■) and temperature ranges, according to time of day, in a University of Maryland study population of healthy adults [4]. The four temperatures (°C [°F]) shown at each sample time are the 99th percentile (*top*), 95th percentile (*second*), mean (*third*), and 5th percentile (*bottom*) for each sample set. The numbers in parentheses on the *x* axis indicate the number of observations analyzed at each sample time. (Reprinted from [4] with permission.)



Comparisons of simultaneously obtained oral, axillary, and rectal temperature recordings in groups of elderly and young subjects have shown lower average oral and axillary temperatures in elderly subjects but comparable average rectal temperatures in the two groups [21]. In view of these findings, it seems that, in general, the elderly exhibit lower "body" temperatures than younger counterparts if axillary or oral readings are used as measures of body temperature but not if rectal readings are used.

Some authors believe that the first temperature reading obtained on admission to a hospital can be falsely elevated, because stress, in the broadest sense, has the capacity to elevate body temperature [6, 16]. The University of Maryland study described above did not find evidence that the first temperature reading obtained after admission to a research study unit was less reliable than measurements obtained at later times [4]. Maryland investigators, however, could not be certain that stress levels at the time of admission to their unit were comparable to levels of stress experienced by patients at the time of admission to a hospital.

As a result of work conducted earlier this century [22, 23], it is widely believed that heart rate increases by 10 beats for each 1°F rise in body temperature. Data obtained in the University of Maryland survey indicate that heart rate increases only 2.44 beats for each 1°F rise in temperature [4]. The difference between the earlier and more recent investigations most likely reflects the fact that in the latter instance, subjects were afebrile and were examined while seated, whereas those examined in earlier investigations were mostly febrile and reclined on a couch for 20 minutes prior to examination.

The normal range of body temperature in children is not well delineated. Lorin [24] has written that the range is higher in children than in adults and that a decrease toward adult levels begins at ~1 year of age, continues through puberty, and stabilizes at 13–14 years of age in girls and 17–18 years of age in boys. As documentation of his views on the matter, he offers a 1937 publication by Bayley and Stolz [25]. Unfortunately, these earlier investigators did not control for variables such as time of day, bundling, and thermometer dwell-time, each of which might have significantly affected the results of their survey. It has also been maintained that the circadian rhythm that characterizes body temperature in the adult is less evident in the first few months of life, well established by the second birthday, and more pronounced during childhood than during adulthood [24]. This concept, like many concerned with the normal temperature of children, is difficult to substantiate with published data.

Fever Patterns—Theodore E. Woodward, M.D.

Attempts to derive reliable and consistent diagnostic clues from evaluation of the febrile record, per se, are fraught with uncertainty. Accuracy of temperature measurements, use of antipyretics and corticosteroids, and individual variations re-

lated to age, state of hydration, environmental temperature, basal metabolism, and presence of other diseases all influence body temperature. Nevertheless, the following definitions have traditionally been used to categorize febrile patterns into diagnostically useful groups [26].

Continuous (sustained) fever, with slight remissions not exceeding 2.0°F (figure 3). Within this group fall fevers due to lobar and gram-negative pneumonia, the rickettsioses, typhoid fever, CNS disorders, tularemia, and falciparum (malignant tertian) malaria.

Intermittent (septic, quotidian, "picket fence") fever, with wide fluctuations, usually normal or low in the morning and peaking between 4:00 and 8:00 P.M. This group includes fever due to localized pyogenic infections and bacterial endocarditis; chills and leukocytosis are usually present. Malaria (commonly with leukopenia) may present as quotidian (daily spike), tertian (spike every third day), or quartan (spike every fourth day) types. In acute brucellosis, fever is often intermittent, with sweating associated with leukopenia or a normal leukocyte count. A double quotidian pattern, with two daily spikes, occurs sufficiently often to be helpful in diagnosis of salmonellosis, miliary tuberculosis, double malaria infections, and gonococcal and meningococcal endocarditis.

Saddle-back (biphasic) fever: several days of fever, a distinct reduction in febrile levels for ~1 day, and then several additional days of higher fever (figure 4). This type of fever pattern is typical of dengue and yellow fever, Colorado tick fever, relapsing fever, Rift Valley fever, influenza, and other viral infections such as poliomyelitis and lymphocytic choriomeningitis.

Intermittent hectic (Charcot's) fever: sporadic episodes of fever; periods of normal temperature and recurrence of fever. This is a frequent and reliable pattern in cholangitis, usually associated with cholelithiasis, jaundice, leukocytosis, and toxic signs; it may occur in patients without jaundice.

Pel-Ebstein fever, characterized by weekly or longer periods of fever and equally long afebrile periods, with repetition of the cycle (figure 5). It occurs in Hodgkin's disease, brucellosis due to *Brucella melitensis*, and relapsing fever. Occasionally in tuberculosis, the febrile course may be similarly intermittent.

Reversal of diurnal pattern of fever (typhus inversus), with the highest temperature elevation in the early morning hours rather than during the late afternoon or early evening. Occasionally in miliary tuberculosis, salmonellosis, hepatic abscess, and bacterial endocarditis there is reversal of the usual diurnal pattern of fever.

Jarisch-Herxheimer reaction, with sharply increased elevation of temperature and exacerbation of other clinical abnormalities. This occurs several hours after the beginning of penicillin treatment for primary or secondary syphilis, in leptospirosis and tick-borne relapsing fever, and also following tetracycline or chloramphenicol therapy for acute brucellosis.

Is the fever curve useful clinically as an aid to diagnosis? If so, how can it best be utilized for this purpose? Careful

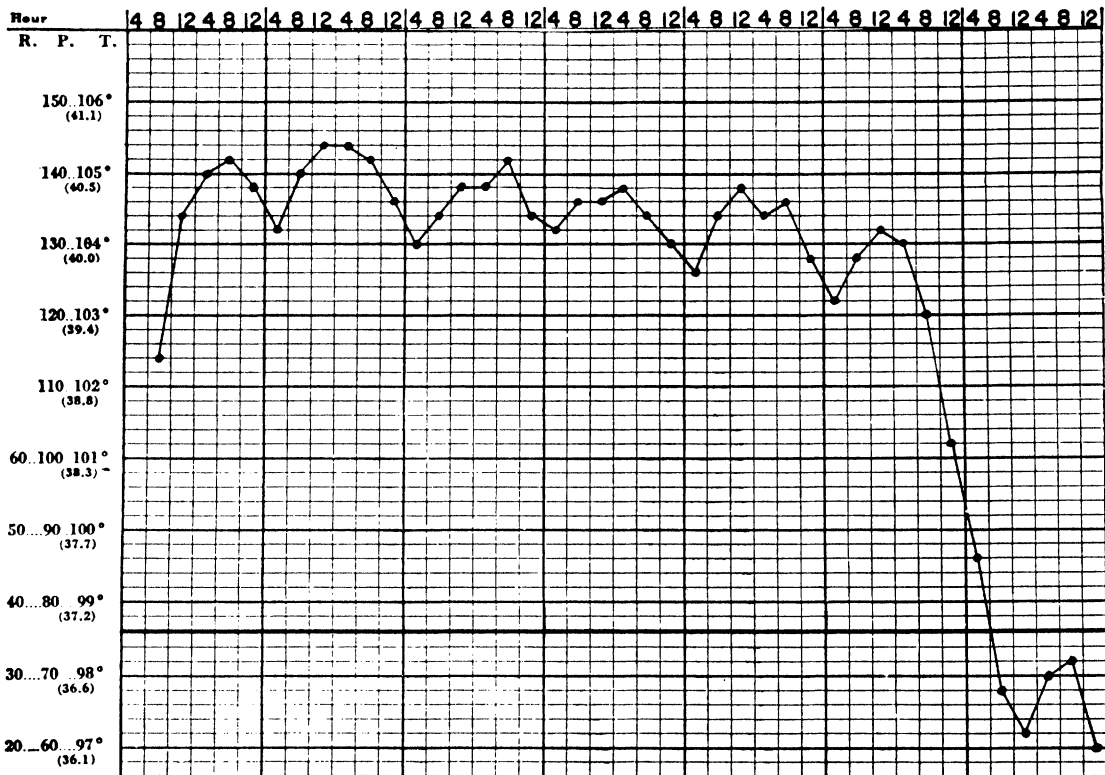


Figure 3. Plot of a continuous fever, ending by crisis, in a patient with lobar pneumonia. (Reprinted with permission from Kampmeier RH, Blake TH. Physical examination in health and disease. 4th ed. Philadelphia: FA Davis, 1970:124-5.)

scrutiny of fever patterns to a certain extent simulates gazing at the Rockettes. In some respects, each is similar to the other, but careful evaluation reveals distinct differences not only in shape but in topography, uniformity, and rhythm. However,

such differences are subtle and will rarely be detected unless time is taken to plot the fever curve on a continuous graph.

In evaluation of a febrile illness, the mere contour of a daily fever pattern, coupled with chills, the presence or absence of

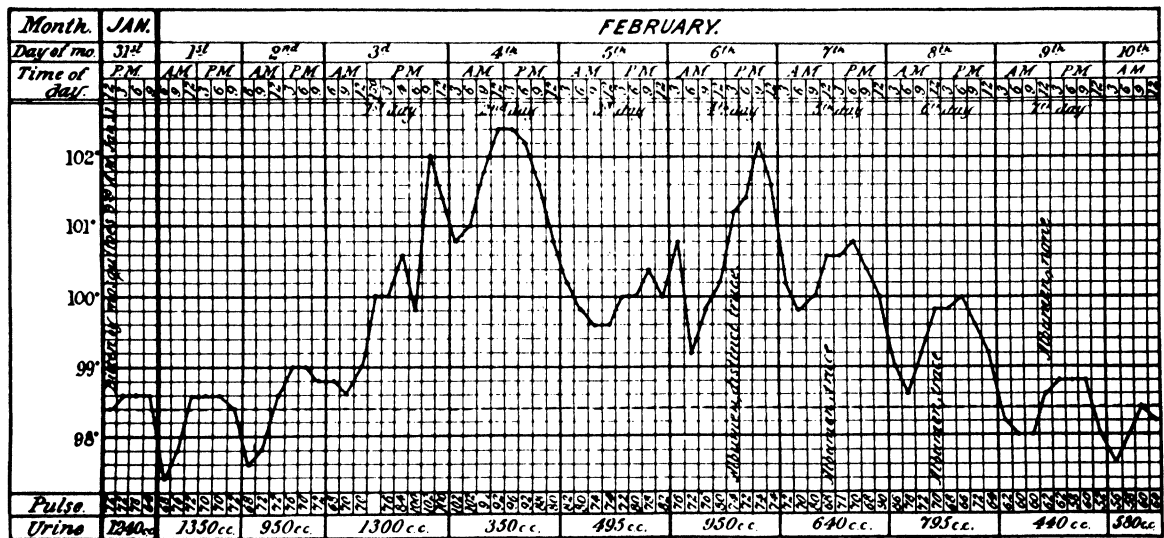


Figure 4. Plot of a saddle-back (biphasic) fever in a patient with yellow fever. (Reprinted from Reed W., et al. Experimental yellow fever. Am Med 1901;III:12.)

a rash at a specified time, the nature of the rash, the blood leukocyte count, and the manner in which the fever responds to treatment each have diagnostic relevance. For this reason, one should not be satisfied simply with recognizing the existence of a fever. The manner in which the fever begins and when it peaks (A.M. or P.M.) are helpful and, like those features described above, may assist the alert clinician in the diagnosis of obscure febrile illnesses.

The Pyrogenic Cytokines—*Jeffrey D. Hasday, M.D., and Simeon E. Goldblum, M.D.*

The cytokines are a diverse group of polypeptide hormones with a variety of names, including “interleukins,” “growth factors,” “interferons,” and “tumor necrosis factors.” This complex and often confusing nomenclature evolved because names of individual cytokines were initially based on only one of what eventually proved to be a wide array of bioactivities. Fortunately, molecular techniques now offer a more precise means of categorizing and identifying cytokines.

Full understanding of cytokine physiology is complicated by the fact that individual cytokines often influence expression of other cytokines and/or their receptors and may induce more distal co-mediators of cytokine-induced bioactivities (e.g., prostaglandins and platelet-activating factor). Therefore, it is not always possible to assign direct or intrinsic *in vivo* bioactiv-

ities to given cytokines with certainty. Such difficulties notwithstanding, several cytokines have been functionally grouped together on the basis of pyrogenic activity. In the future, this group of so-called pyrogenic cytokines will surely grow and some current members may be deleted.

Currently recognized pyrogenic cytokines include IL-1 (IL-1 α and IL-1 β), TNF- α , IL-6, and IFN (table 2) [27–35]. Even within this small group of cytokines, complex relationships exist, with various members upregulating or downregulating expression of other members or their receptors under certain conditions. The four pyrogenic cytokines have a monomeric molecular weight range of 17–30 kD, are undetectable under normal conditions in healthy subjects, and are produced in a wide range of tissues in response to diverse stimuli. Once released, such molecules have short intravascular half-lives. Pyrogenic cytokines are pleiotropic, recognizing receptors on multiple host target tissues. They are active in picomolar quantities and induce maximal cellular responses, even at low receptor occupancy. After release, such cytokines can be found in virtually all body fluids and exert local (autocrine/paracrine) as well as systemic (endocrine) effects.

The pivotal function of pyrogenic cytokines or “endogenous pyrogens” in mediating the febrile response has recently been reviewed by Kluger [36], who proposed a series of five Koch’s postulate-like criteria for defining endogenous pyrogens. It is interesting that of the four pyrogenic cytokines included in our discussion, only IL-6 satisfied all five criteria. According to

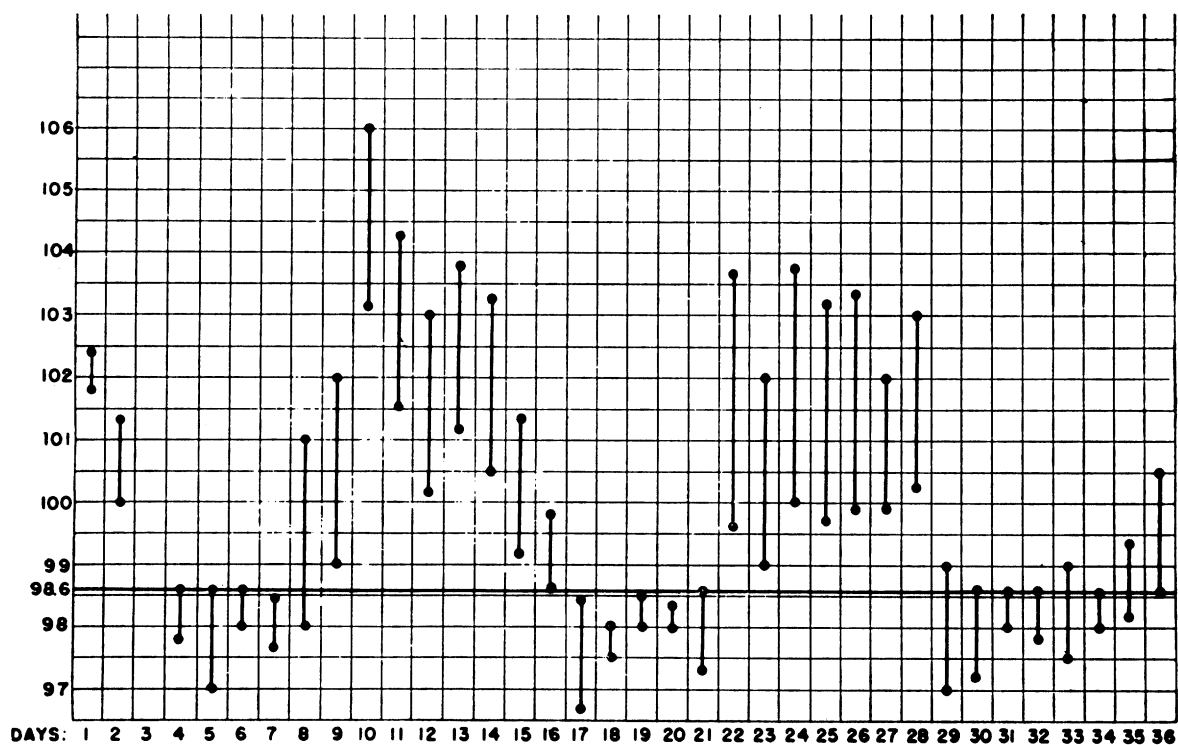


Figure 5. Plot of a Pel-Ebstein fever in a patient with Hodgkin’s disease. (Reprinted with permission from Kampmeier RH, Blake TH. *Physical examination in health and disease*. 4th ed. Philadelphia: FA Davis, 1970:124–5.)

Table 2. Characteristics of currently recognized pyrogenic cytokines.

Cytokine	Aliases	Sources	Factors upregulating	Factors downregulating	Effect on other pyrogenic cytokines	Bioactivities (induced or co-mediated)
IL-1	Lymphocyte activating factors, endogenous pyrogen, leukocyte endogenous pyrogen, mononuclear factor, catabolin, osteoclast activating factor, hematopoietin-1, melanoma growth inhibition factor, tumor inhibitory factor-2	Monocytes, macrophages, astrocytes, endothelial cells, keratinocytes, dendritic cells, fibroblasts	LPS, IL-1, TNF, IFN- γ , GM-CSF, zymosan C5a, leukotrienes, PMA	Corticosteroids, PGE ₂ , IL-4, IL-6, IL-10, TGF β , retinoic acid	\uparrow TNF, \uparrow IL-1, \uparrow IL-6,	Induction of acute-phase response, T-cell activation, IL-2/IL-2R induction, thymocyte costimulation, fibroblast activation, costimulation of B cell proliferation and differentiation, augmentation of CTL and LAK induction, induction of endothelial adhesion molecules, enhancement of phagocyte microbial killing, acceleration of wound healing
TNF- α	Cachectin	Monocytes, macrophages, eosinophils, neutrophils, lymphocytes, astrocytes, endothelial cells, mast cells, Kupffer cells, NK cells, some tumors	Bacteria, viruses, fungi, protozoa, LPS, staph TSST1, IL-1, IL-2, TNF, IFN, GM-CSF, PAF, substance P, anti-TCR antigen, tumor cells, PMA	Corticosteroids, cyclosporin A, PGE ₂ , IL-4, IL-6, IL-10, TGF β , vitamin D ₃	\uparrow TNF, \uparrow IL-1, \uparrow IL-6	Septic shock, tumor killing and cytostasis, enhancement of phagocyte microbial killing, tumor necrosis, cachexia, anorexia, endothelial/epithelial MHC and adhesion molecule induction, osteoclast activation, B cell differentiation, CTL induction
IL-6	IFN- β 2, 26-kD protein, B cell stimulatory factor-2, hybridoma/plasma-cytoma growth factor, hepatocyte stimulating factor, cytotoxic T cell differentiation factor, macrophage granulocyte inducing factor 2A	Monocytes, macrophages, B or T cells, fibroblasts, endothelial cells, epithelial cells, keratinocytes, bone marrow stroma, some tumors	LPS, IL-1, TNF, IFN- β , calcium ionophore, mitogenic viruses	Corticosteroids, estrogens	\downarrow TNF, \downarrow IL-1	B cell growth and differentiation, IgG synthesis, myeloma proliferation, CTL induction, acute-phase response, thymocyte costimulation, weak antiviral activity, megakaryocyte maturation, neuronal differentiation, enhancement of IL-3-dependent stem cell proliferation
IFN	Type II IFN, immune IFN	T cells, NK cells	Mitogenic lectins, antigen, IL-1, IL-2	Corticosteroids, cyclosporin A, vitamin D ₃	\uparrow TNF, \uparrow IL-1	Macrophage priming, antiviral activity, enhancement of TNF activity, MHC induction, enhancement of NK activity, enhancement of endothelial ICAM-1 expression, inhibition of IL-4-induced B cell responses, B cell differentiation and IgG2a secretion

NOTE. C5a = complement component C5a; CTL = cytotoxic T-lymphocytes; GM-CSF = granulocyte/macrophage colony stimulating factor; ICAM-1 = intracellular adhesion molecule-1; IL-2R = recombinant interleukin-2; LAK = lymphokine-activated killer cell; LPS = lipopolysaccharide (bacterial); MHC = major histocompatibility complex; PAF = platelet activating factor; PGE₂ = prostaglandin E₂; PMA = phorbol myristate acetate; staph TSST1 = staphylococcal toxic shock syndrome toxin-1; TCR = T-cell reactivity; TGF β = transforming growth factor β ; \uparrow = enhanced expression; \downarrow = inhibited expression.

current concepts, exogenous and/or endogenous stimuli initiate the febrile response by being presented to specialized host cells that, in turn, respond by synthesizing and releasing specific amounts of various pyrogenic cytokines into the circulation (figure 6).

In a given host, a particular exogenous pyrogen (e.g., LPS or a virus) promotes release of its own characteristic pattern and concentration of cytokines. The pyrogenic cytokines themselves have the capacity to both upregulate and downregulate their own expression, as well as that of other cytokines. Ultimately, each cytokine recognizes and binds to its own specific receptors, the most important of which—at least in terms of their thermoregulatory effects—are located on neurons in close

proximity to the preoptic region of the anterior hypothalamus (figure 6), particularly in the area proximal to the organum vasculosum lamina terminalis [36]. Here, the cytokine-receptor interaction activates phospholipase A₂, resulting in liberation of plasma membrane arachidonic acid as substrate for the cyclooxygenase pathway.

Some cytokines appear to increase cyclooxygenase expression directly, leading to liberation of an arachidonate metabolite, prostaglandin (PG) E₂. This small lipid mediator easily diffuses across the blood-brain barrier, where it and perhaps other pyrogenic factors influence the responsiveness of the thermosensitive neurons that the thermoregulatory center comprises. Although not discussed here, recent studies indicate that thermal

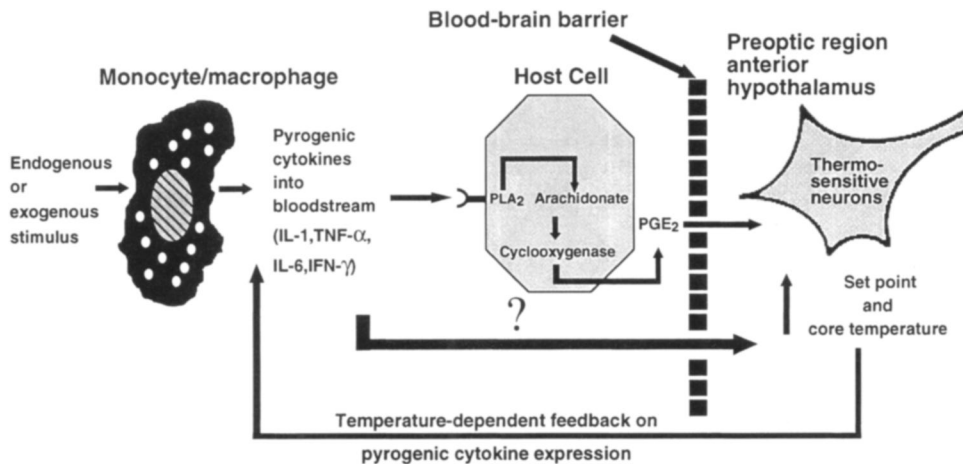


Figure 6. Mechanisms, mediators, and critical cell participants of the febrile response (PLA₂ = phospholipase A₂).

information involved in the febrile response might also be transmitted from the periphery to the thermoregulatory center via peripheral nerves.

Several counterregulatory feedback mechanisms have been proposed for the attenuation of pyrogenic cytokine expression and fever. While PGE₂ acts centrally to induce fever, it also appears to downregulate pyrogenic cytokine gene expression in the periphery. Corticosteroids have a similar inhibitory effect on cytokine gene expression and phospholipase A₂ activity.

Naturally occurring cytokine receptor antagonists provide negative feedback during the febrile response by competing with IL-1 and other pyrogenic cytokines at the receptor level. Endogenous antipyretics such as arginine vasopressin and α -melanocyte-stimulating hormone appear to provide a similar service during episodes of fever [37].

Although work on pyrogenic cytokines over the past 2 decades has provided a hypothetical model for the febrile response, our understanding of this process remains incomplete and largely speculative. It is not known, for instance, whether circulating cytokines cross the blood brain barrier; if cytokines produced within the CNS are necessary for the febrile response; if local mediators other than PGE₂ are involved in fever; what determines the magnitude of expression of individual cytokines to various stimuli; or how the upper limit of the febrile range is set.

Although TNF- α and IL-1 play a pivotal role in initiating the febrile response [36], they also continue to be expressed throughout episodes of fever [38]. A small but growing body of literature suggests that elevated temperatures near the upper end of the febrile range influence expression of such cytokines in vitro and that these effects are highly dependent on experimental conditions [39–46] (summarized in table 3).

The limited data currently available suggest that the in vivo effects of body temperature on cytokine expression are even more complex [47–50]. Although some authors have suggested that modulation of pyrogenic cytokines at febrile-range temperatures might involve the heat-shock response [41, 42], recent

investigations indicate that macrophage TNF- α expression is modulated at temperatures at least 2°C below the heat shock response threshold [45, 46]. Thus, inhibition of TNF- α expression might occur as a component of the heat shock response, but fever might also modulate cytokine expression through a heat shock-independent process.

The Acute-Phase Response—Robert S. Munford, M. D.

Many conditions that elicit fever also trigger production of acute phase proteins (APPs). Indeed, fever and APP synthesis (the acute-phase response) [51] are often considered cardinal components of the general host reaction to both trauma and infection. There are, however, clinical conditions in which fever occurs in the absence of alterations in blood concentrations of APP, and others in which APP levels increase without concomitant fever, suggesting that the febrile and APP responses are independently regulated.

APPs fall into two broad categories: positive and negative. Numerous positive APPs are produced in increased amounts during the acute-phase response [52, 53]. Following major trauma, plasma concentrations of such proteins may increase less than 4-fold (e.g., ceruloplasmin, haptoglobin) or as much as 1,000-fold (e.g., C-reactive protein [CRP] and serum amyloid A). The rate of change in plasma concentration is also variable, with CRP and serum amyloid A levels increasing and decreasing more rapidly than, for example, levels of fibrinogen or complement factors. Fewer negative APPs have been identified. Of these, albumin is the most prominent, although plasma concentrations of transferrin and transthyretin (prealbumin) also decrease during the acute-phase response.

Most APPs are synthesized in the liver. Such synthesis is regulated by circulating cytokines and hormones, which induce specific transcription factors to activate (or inhibit) the promoter/enhancer domains of individual APP genes, thereby modulating gene transcription [53, 54]. Synthesis of many APPs is also regulated by posttranscriptional mechanisms, such

Table 3. Effects of hyperthermia on pyrogenic cytokine expression in vitro.

Reference	Cell source	Hyperthermia			Effect on expression
		Acute/chronic*	Temperature (°C)	Timing†	
[39]	Mouse BCG-PM‡	A	40.5–43	1.5–4 h	↑TNF
		A	42–43	0	↓TNF
		C	39	1.5 h	↑TNF
	Human PBMC§	A	40.5	–1 h	↑TNF
			≥42	–1 h	↓TNF
[40]	Mouse BCG-PM	A	40.5–43	2–4 h	↑TNF
[41]	TG-PM	A	≥41	–20 m	↓TNF
[42]	TG-PM	A	45	–12 m	↓TNF
[43]	Astroglial cells	C	40	0	↓TNF, IL-1
[44]	Human PBMC	C	39	0	↓IL-6; NC in IL-1 or TNF
[45]	Human PBM-MØ¶	C	38.5–40	–0.5–0 h	↓TNF; NC in IL-6
[46]	Raw 264.7	C	40	–0.5 h	↓TNF

NOTE. ↑ = enhanced; ↓ = inhibited; NC = no change.

* Chronic (C) indicates entire incubation was performed at the indicated elevated temperature; acute (A) indicates temperature was returned to 37°C after exposure to indicated temperature.

† Elapsed time between LPS addition and temperature shift. Minus signs indicate temperature shifts occurred before addition of LPS.

‡ Peritoneal macrophages from mice with BCG.

§ Peripheral blood mononuclear cells.

|| Peritoneal macrophages from mice primed with thioglycolate.

¶ Human monocyte-derived macrophages.

as mRNA stabilization [55], enhanced translation [56], and release of APPs stored in the endoplasmic reticulum [57].

A complex mixture of hormones regulates APP synthesis. While IL-6 plays a prominent role in this process [58–65] (table 4), it is not the only important agonist. For example, mice deficient in IL-6 do not increase APP production in response to TNF- α , IL-1 β , or turpentine-induced abscess [64, 65], but they do respond to bacterial LPS by greatly elevating APP blood levels [64]. The possibility that LPS might elicit APP synthesis directly, rather than via circulating cytokines other than IL-6, was not addressed in these studies [64]. Nevertheless, one may conclude tentatively that the relative importance of IL-6 in mediating APP responses depends upon the nature of the inflammatory stimulus.

Other studies have found that APP production can be partially inhibited by monoclonal antibodies to TNF- α [66] or IL-1 β [67], suggesting that TNF- α and IL-1 may also elicit APP production, perhaps in conjunction with IL-6. Whereas glucocorticoids in physiological amounts are required for APP

synthesis, high doses of exogenous glucocorticoid can inhibit APP production in response to inflammatory stimuli [68, 69]. Insulin, IL-4 [70], IL-1 receptor antagonist (IL-1Ra), and α -melanocyte-stimulating hormone [71, 72] also inhibit APP synthesis under certain conditions.

Such inhibition may be direct and/or indirect. Recombinant IL-4, for example, elicits large increases in circulating IL-1Ra in vivo in humans [73], while it inhibits in vitro APP production by hepatocytes in response to IL-6 [70] and antagonizes the production of IL-6, TNF- α , and IL-1 β by monocytes [74]. Interleukin-10, which inhibits numerous proinflammatory responses of macrophages [75] and other cells, also appears to blunt APP production by indirectly augmenting IL-1Ra production [76].

Both agonists and antagonists may have different effects on production of individual APPs. At least in vitro, proinflammatory cytokines such as IL-1 and TNF increase production of type 1 APPs (CRP, serum amyloid A, α 1-acid glycoprotein, and others), while IL-6 induces production of type 2 APPs (fibrinogen, haptoglobin, and certain antiproteases) and can cooperate with IL-1 and TNF to induce type 1 APPs [53]. Similarly, IL-1Ra blocks production of CRP and serum amyloid A by LPS-stimulated human Hep 3B cells, while having no effect on production of α 1-protease inhibitor and increasing production of fibrinogen [77]. Most clinical studies have measured CRP, the APP with the greatest dynamic range and yielding the best quantitative assay results. Unfortunately, predicting changes in the other positive APPs from the behavior of CRP is not possible.

Table 4. IL-6 and acute-phase protein (APP) regulation.

- IL-6 levels correlate with APP levels in various clinical states.
- Intravenously administered IL-6 elicits APP production in vivo [58].
- Monoclonal antibodies to IL-6 decrease APP production in response to turpentine abscess in vivo [59, 60] and in humans with multiple myeloma [61], Castleman's disease [62], and rheumatoid arthritis [63].
- Disrupting the murine IL-6 gene greatly reduces APP production in response to turpentine abscess [64], TNF- α , and IL-1 β [65].

Defining specific roles for cytokines and related molecules in human APP production has been difficult. Despite convincing evidence that IL-1Ra modulates APP production in mice with turpentine abscesses [78], for example, IL-1Ra has no apparent effect on the CRP response to low-dose endotoxin infusion in volunteers [79]. Although there may be a simple explanation for this discrepancy (different inflammatory stimuli with differing importance of IL-1 in APP production), such data raise serious questions about the relevance of results of animal studies of APP to human diseases.

Fever and APP production are both components of the acute-phase response, but can one occur without the other? In both experimental animals and humans, blocking elevation in core temperature during the febrile response with cyclooxygenase inhibitors has little or no impact on the normal APP response [80]. Elevation in core temperature per se is therefore not required for normal APP regulation. Is it sufficient? Does fever induce APP production? Intracerebral injection of low doses of TNF and IL-1 induces fever without increasing APP production in mice, whereas higher doses of these cytokines elicit both fever and APP synthesis [71].

van Vugt and colleagues [81] have reported that hyperthermia and intracerebroventricular injection of PGE₂ elicit similar APP responses in rats. Both adrenalectomy and alpha- and beta-adrenergic blockade prevented the APP response but had no effect on PGE₂-induced fever. Because adrenaline is a potent stimulus for IL-6 production in rats [82], these same investigators have proposed that hyperthermia (or other stress), by raising circulating concentrations of adrenaline, elicits IL-6 production, which mediates augmented production of positive APPs.

Although the role of adrenalin in APP regulation in humans is uncertain, these observations in rats suggest that APP production should normally accompany the stress of fever or hyperthermia. As will be discussed below, exceptions to this generalization provide some of the best available evidence that endogenous inhibitors of APP synthesis are clinically important.

Can any of the APPs induce fever? Recent reports would suggest not. In fact, it has been shown that serum amyloid A inhibits fever induced by TNF- α or IL-1 β in mice [83] and that CRP and other APPs, by increasing the synthesis of IL-1Ra in response to various agonists [84], might also have an indirect antipyretic effect.

Febrile patients usually have increased levels of one or more positive APPs, and patients with elevated levels of APPs usually have at least modest elevations in body temperature at some time during the course of their illness. The distinction drawn here is that there are clinical situations in which the increase in APP production (in most instances, the data are limited to CRP) and the degree of fever are less than might be anticipated from the overall severity of the ongoing inflammatory response. Such situations provide further evidence that fever and APP production are independently regulated in humans.

Both APP production and fever are found in most invasive bacterial diseases. An elevated plasma CRP concentration is said to be highly suggestive of bacterial infection in children with illnesses of ≥ 12 hours' duration [85]. In children with meningitis, a serum CRP level of >20 mg/L strongly suggests a bacterial etiology [86]. Viral illnesses are generally associated with much smaller increases in CRP, although there is overlap with bacterial infections [87]. Extensive, acute thermal injury is another condition in which an elevated core temperature is closely associated with APP production, provided sufficient time has elapsed for the APP response to occur [88, 89].

In other conditions, APP production may occur without fever. For example, major surgery typically triggers vigorous APP production. CRP levels peak 2–3 days after surgery and decline thereafter, usually approaching normal by postoperative day 7 [90–92]. CRP elevations of lesser magnitude are frequent following myocardial infarction [93]. A recent report has also described slightly increased CRP levels in patients with unstable angina that progresses to myocardial infarction [94]. Many other conditions involving the musculoskeletal system also induce APP production, even when fever is minimal or absent. These include chronic osteomyelitis, vertebral diskitis, prosthetic joint infections [95], rheumatoid arthritis [96, 97], spondyloarthropathies (psoriatic arthritis, ankylosing spondylitis), polymyalgia rheumatica, and multiple myeloma.

In patients with rheumatoid arthritis, CRP may be a useful marker for disease activity [96]. Although glucocorticoid therapy often reduces CRP levels directly, cyclooxygenase inhibitors (except for prinomide) appear to do so only when disease activity also diminishes [96, 98, 99].

In other clinical circumstances, fever may not be accompanied by APP production. Most interesting in this regard are a number of febrile viral and parasitic diseases in which there is little or no evidence of APP production. Trichinosis, for example, is characteristically associated with a normal erythrocyte sedimentation rate. The explanation for the lack of enhanced APP production during trichinosis is unknown. Helminthic infections typically induce a T-helper lymphocyte-2 immune response, in which IL-4 and IL-10 predominate, but other factors are also involved in the response. In rats, gastrointestinal infections with *Nippostrongylus brasiliensis* and *Trichinella spiralis* fail to induce APP production, while systemic infection with *N. brasiliensis* elicits brisk APP synthesis [100].

Marrow transplant recipients who develop fever during graft-versus-host disease typically do not have elevated CRP levels [101, 102]. Although the explanation for this finding has yet to be determined, one small study found that whereas such patients do not exhibit elevations in circulating IL-6 [102], they usually have (often strikingly) elevated IgE levels, perhaps due to the activity of IL-4 [103]. As noted above, recombinant IL-4 induces minimal elevations of CRP levels in volunteers, while causing a marked increase in IL-1Ra levels [73].

Unlike patients with other connective tissue diseases, patients with systemic lupus erythematosus often do not mount

much of a CRP response, even during acute exacerbations of their illness [104]. Lower-than-expected CRP and fibrinogen levels exist in the presence of high circulating IL-6 concentrations [105], suggesting that production of APP does not occur despite proinflammatory stimuli.

A potential explanation for this apparent paradox comes from experimental studies in mice [106]. Whereas TNF- α is an important proinflammatory cytokine in murine collagen II-induced arthritis (a model for rheumatoid arthritis), it prevents NZB/W F₁ mice from developing lupus. IL-10, by comparison, opposes the inflammatory actions of TNF α in murine rheumatoid arthritis, while accelerating murine lupus. In keeping with a role for IL-10 in human systemic lupus erythematosus, recent data indicate that peripheral blood mononuclear cells from untreated patients with the disease secrete large amounts of IL-10 in vitro and that immunoglobulin production by the lupus-associated B lymphocytes is largely IL-10-dependent [107]. If IL-10 is a dominant cytokine in human lupus, it might indirectly reduce CRP production. Although patients with rheumatoid arthritis frequently have elevated serum and synovial fluid IL-10 levels [108], a complex mixture of factors most likely regulates specific responses.

Patients with polymyositis/dermatomyositis, like those described above, do not exhibit expected elevations in circulating CRP during exacerbations of their disease. A recent study [109] found that such patients have higher blood concentrations of IL-1Ra and soluble TNF receptors (55 and 75 kD) than do patients with spondyloarthropathy, who have significantly higher CRP levels. Serum CRP and IL-6 levels correlated positively in the patients with spondyloarthropathy but not in patients with polymyositis/dermatomyositis. In the latter patients, the circulating APP inhibitors (IL-1Ra, TNF receptors) thus seemed to dominate the agonists studied (IL-6, TNF- α).

In conclusion, many factors appear to influence fever and APP synthesis. Circulating concentrations of agonists and inhibitors (the mediator "mix") seem most important, yet the ways in which these molecules interact to regulate APP production and body temperature in vivo are poorly understood. Nevertheless, the existing data leave little doubt that these two components of the host inflammatory response are regulated independently, a fact that makes CRP measurements useful in several clinical situations (table 5).

Fever Therapy: Lessons for the Future—Paul D. Stolley, M.D., M.P.H.

There have been many attempts in the past to employ induced fever as a therapeutic agent. Indeed, the 1927 Nobel Prize in Medicine was won by Julius Wagner-Jauregg for his work with fever therapy in the treatment of chronic syphilis infections of the CNS [110].

The regimen pioneered by Wagner-Jauregg was severe, requiring several days of high fever produced by the injection

Table 5. Some clinical uses of quantitative serum CRP measurements (determined by rate nephelometry, with use of the international standard) [87].

-
- In marrow transplant recipients with fever, a CRP level >20 mg/L suggests infection rather than graft-vs.-host disease [101, 102].
 - In the absence of serositis, a CRP level >60 mg/L in a febrile patient with systemic lupus suggests concurrent infection [104].
 - In patients with rheumatoid arthritis, CRP levels often correlate directly with disease activity and decrease in response to effective therapy [96].
 - Serial measurements of serum CRP levels may help predict or diagnose infectious complications in patients postoperatively [90–92].
 - Monitoring CRP levels may be useful for following the resolution of pyelonephritis, meningitis, or pelvic infections (reviewed in [87]).
 - A consistently normal CRP level is evidence against most inflammatory disorders (with the possible exceptions of systemic lupus erythematosus and ulcerative colitis).
 - An elevated CRP level favors a bacterial over viral etiology of meningitis in children [86].
-

of live malarial parasites, ultimately terminated with quinine. More than a hundred different case-series were published, reporting good results; dissenting reports were rare. Since no randomization, double-blinding, or controls were used (because the technique of the randomized controlled trial had not yet been described for most of this period), the efficacy of fever therapy in syphilis is still unknown.

Fever therapy is experiencing a revival of sorts in the treatment of AIDS and chronic sequelae of Lyme disease. In addition, there is mounting interest in the therapeutic application of several of the pyrogenic cytokines (see below). Although preliminary data suggest that such therapies have merit, carefully controlled, randomized, double-blind trials of such treatments must be conducted if we are to avoid the kind of uncertainty that continues to plague modern-day assessment of Wagner-Jauregg's highly acclaimed treatment for chronic CNS syphilis.

Therapeutic Uses for Pyrogenic Cytokines—Ernest C. Borden, M.D.

Of the major pyrogenic cytokines, the IFNs have enjoyed the widest application as therapeutic agents. IFNs typify lymphokines and cytokines that modify the host response to microbial and neoplastic diseases. As human proteins, they differ both chemically and biologically from most other therapeutic molecules.

IFNs were the first lymphokines or cytokines produced by recombinant DNA technology and, indeed, the first such proteins used therapeutically (the first protein actually produced by recombinant DNA technology for therapeutic use was insulin). Substantial preclinical work initially focused on the antiviral activity of IFNs; they are now used clinically in >50 countries for the treatment of viral and neoplastic diseases [111, 112].

IFNs are among the most potent of gene modulators, with the possible exception of glucocorticoids. Like the production of other cytokines, IFN production is tightly modulated. More than 30 genes and their protein products are involved in the production of IFNs [113], including 2-5A synthetase and protein kinase, as well as other lymphokines and cytokines. IFNs are not constitutively expressed; rather, they are produced only in response to specific triggers such as double-stranded RNA or specific antigens.

In the earliest clinical trials of IFNs [114], fever was recognized as a frequent side effect. Almost all patients develop fever on the initial day of IFN treatment, and such fever likely represents one aspect of the broad cellular actions of IFNs. The initial material, produced from human buffy coat blood donor units, was highly purified (~90%). However, not until the introduction of IFNs produced by recombinant DNA technology, purified to homogeneity and proven to be endotoxin-free, was it clear that fever is a side effect of the IFN molecule itself [115, 116].

In a phase I clinical trial of IFN- β , 12 of 13 patients had a fever on the initial day of treatment; by the fifth day of daily injections, only 3 of the 13 patients had a temperature $>37.5^{\circ}\text{C}$ [117]. This gradual diminution in pyrogenicity is one of the hallmarks of IFN therapy, a characteristic not shared by therapy with other pyrogenic cytokines. For example, in a phase II clinical trial of IL-2—another pyrogenic lymphokine licensed for therapeutic use—26 of 28 patients treated with IL-2 developed a fever (temperature of $\geq 39^{\circ}\text{C}$) [118], which did not resolve with repetitive dosing.

Temperature on the initial day of IFN therapy characteristically reaches a height of $38\text{--}39^{\circ}\text{C}$ orally, 5–6 hours following IFN administration, and the fever persists for ~2 hours. It is usually preceded by mild chills and malaise. However, in contrast to other lymphokines such as TNF [119], the IFNs only occasionally cause rigors.

The pyrogenicity of IFN is generally dose-related, as is modulation of gene expression [117, 120]. However, temperature elevations caused by IFN are characterized by substantial individual variability. It is interesting that production of lymphokines and cytokines such as IL-1 β and colony stimulating factor-G is enhanced at temperatures at the upper end of the febrile range, whereas TNF production is suppressed [121].

Hyperthermia itself augments the effects of IFNs both in vitro and in vivo [122, 123]. Because IFN-induced fever resolves with repetitive dosing, it is not the most troublesome side effect of IFN therapy. Fatigue and anorexia are the primary dose-limiting side effects. The physiological mechanisms responsible for these adverse effects are poorly understood.

In contrast with other lymphokines and cytokines, the hematoopoietic cytokines cause little elevation in temperature. Thus, each lymphokine and cytokine (including the various IFNs) exhibits its own characteristic pyrogenic response [116]. Two α IFNs produced by recombinant DNA technology exhibited different degrees of pyrogenicity on clinical testing at equivalent doses. The mean maximum temperature following treat-

ment with IFN- α_1 was $\sim 1^{\circ}\text{C}$ lower than that following treatment with IFN- α_2 .

In these studies, eight patients treated with IFN- α_1 required 1,300 mg of acetaminophen to control fever, vs. the 4,875 mg required by those treated with IFN- α_2 . Despite these differences in pyrogenicity, the two IFNs were equivalent in their capacity for augmenting 2-5A synthetase activity and potentiating NK cell cytotoxicity.

In addition to modulating gene expression, IFNs and other cytokines stimulate glucocorticoid secretion. Patients given IFN- β exhibit ~2-fold increases in serum adrenocorticotrophic hormone and cortisol levels 60–120 minutes before the onset of fever [124]. The anterior pituitary hormones, growth hormone and prolactin, are also stimulated ~2-fold in a manner similar to that observed after treatment with TNF [124]. Since the rise in glucocorticoids occurs prior to the onset of fever induced by IFNs and cytokines, it does not appear to be caused by the fever. Nevertheless, hormonal responses, like fever, diminish with repetitive IFN treatments.

When recombinant IFNs were introduced into clinical trials in 1981, it was not clear whether a therapeutic role would even be identified for such molecules. IFNs are now licensed for the treatment of numerous viral and neoplastic diseases and for multiple sclerosis. In addition to antiviral and pyrogenic activities, IFNs also have antiproliferative, antiangiogenic, and immunomodulatory effects. They are currently among the top 10 drugs sold worldwide.

Thus, 15 years after the introduction of IFNs into clinical medicine, the question is not whether they are effective therapeutically but rather how they work. Their cellular effects are pleiotropic. It is not known, for example, whether papillomavirus clinical syndromes, which can be treated effectively with IFNs, improve as a result of their antiviral effects or regress because of their immunologic, antiangiogenic, or antiproliferative effects. Considerably more work must be done to elucidate such mechanisms, as well as those responsible for side effects such as fever, and to determine how to reduce the toxicity of such agents without compromising their therapeutic activity.

Pyrogenic Cytokine Inhibitors: Clinical Applications— Stanley A. Nasraway, M. D.

An expanding array of scientific data suggest that pyrogenic cytokines such as TNF and IL-1 mediate at least some of the pathophysiological derangements of septic shock [125]. As a result, there has been intense interest in the treatment of severely septic patients with agents capable of inhibiting pyrogenic cytokines.

One such agent, IL-1Ra, is released in quantities ~100-fold greater than those of IL-1 itself following experimental endotoxin challenge [126] and in even greater quantities (7,000 \times) during human septic shock [127]. It is believed that this naturally occurring receptor antagonist is part of a system of checks and balances within the host inflammatory response.

Although initial efforts to test IL-1Ra in bacterial and fungal sepsis looked promising [128], more rigorous study of >1,400 patients with sepsis syndrome during phase IIIa and IIIb trials failed to demonstrate a statistically significant improvement in survival rates with such treatment [129, 130]. Retrospective subgroup analysis surprisingly revealed a paradoxical increase in IL-1 serum concentrations following IL-1Ra administration [131], underscoring the present limitations in our understanding of the cytokine network.

Attempts to attenuate TNF activity *in vivo* have followed two paths: neutralization of endogenous TNF via monoclonal antibodies and dilution of TNF activity via soluble receptors. The latter concept has been tested in a phase II trial using a p75 receptor/fusion construct. Unfortunately, mortality was greater among patients receiving high doses of soluble TNF receptor than among controls; as a result, further testing was abandoned (Immunex, data on file).

It was subsequently demonstrated in a murine model of gram-negative sepsis that p75 receptor administration is associated with prolonged and tonic release of TNF, potentially aggravating the inflammatory response [132]. Human testing of another fusion construct, the p55 receptor, is ongoing (Hoffmann-LaRoche, data on file).

NORASEPT I (North American Anti-TNF Sepsis Trial I), a trial of murine monoclonal antibody to TNF involving 971 patients with sepsis syndrome, found no overall improvement in survival rate among treated subjects [133]. However, in a prospectively designed subanalysis of patients in shock, treatment was associated with an improved survival rate, especially in the early period following antibody administration. NORASEPT II, the largest sepsis trial ever undertaken, is presently under way, with the intention of enrolling nearly 2,000 patients with septic shock.

A trial of MAK 195F, a murine IgG to TNF, in the treatment of patients with severe sepsis is also currently under consideration. In this trial, severity of the septic condition is to be monitored by rapid serum assays for IL-6, since IL-6 concentrations have previously been reported to correlate closely with mortality, multiple organ failure, and severity of illness during sepsis [127, 134, 135]. Phase II testing has shown that for patients in whom IL-6 concentrations exceed 1,000 pg/mL, administration of antibody to TNF reduces mortality by >50% (Knoll Pharmaceutical, data on file).

Clinical trials involving inhibitors of pyrogenic cytokines, like those involving monoclonal antibodies to endotoxin, have provided conflicting results. Careful review of such trials suggests that these discrepancies are due, in large part, to problems involved in statistical analysis and experimental design. Such problems include the following.

Failure to discriminate between attributable and nonattributable causes of death. Not all deaths of patients with sepsis are due directly to sepsis; patients with sepsis die from comorbidities and from persistent multiple organ failure, which while associated with sepsis may not be due directly to sepsis. Treat-

ment of sepsis on day 1, for example, is not likely to influence the development of multiple organ failure on day 30. As such, the landmark time point of 28 days mandated by the U.S. Food and Drug Administration is an insensitive, dichotomous parameter of survival that can be skewed by nonseptic events that induce a low "signal-to-noise" ratio. Because not all deaths (as an endpoint) are due directly to sepsis, heretofore many trials have been underpowered, with sample sizes insufficient to discriminate between therapeutic effect and mortality directly attributable to sepsis.

Failure to focus on a narrow cohort of severely ill septic patients with potentially reversible physiological abnormalities, as opposed to an entire septic population in which a large reduction in mortality must be demonstrated in order to prove benefit. The definition of "sepsis syndrome" has been too broad and has led to enrollment of patients with a wide spectrum of severity of illness, with some patients not very ill and others in frank septic shock [129, 136–138]. The heterogeneity of enrolled patients, together with a mixture of comorbidities and conventional treatment approaches, confounds the interpretation of results because of uncontrolled variability and a low signal/noise ratio.

Failure to limit the analytical plan of human sepsis trials to a few, simple, clearly defined endpoints. Subgroup analysis should be preplanned and not, as in some earlier clinical trials, a post-hoc exercise [138].

Failure to recognize the limited applicability of animal models of sepsis. Animal models of sepsis, including direct endotoxin infusion or intravenous bolus bacteremia, do not replicate human sepsis. Tolerance of bacteria and their products varies from species to species; results derived from animal models, therefore, may not necessarily apply to human sepsis. In certain cases, insufficient experimental evidence has been gathered to support hypothetical premises prior to launching human trials [136–139].

Failure to perform an independent statistical analysis by authorities not associated with industry. This was evident during the publication by Centocor of the first phase III trial of HA-1A, a monoclonal antibody to endotoxin. Centocor performed an in-house analysis and misrepresented the true results [139, 140].

Careful clinical trials are important to critically evaluate new immunologic tools such as the pyrogenic cytokine inhibitors. The design of future trials should include the goal of minimizing patient heterogeneity, with an effort to enlist patients most likely to have reversible physiological abnormalities and, hence, most likely to benefit from therapeutic intervention. The corollary to examining a narrow cohort population is the opportunity to limit harm by omitting non-target-population patients. Moreover, there should be an effort not to overinterpret unexpected results, as well as to limit the number of prespecified endpoints and to establish a well-defined target *P* value that is corrected for test multiplicity.

Maximal inflammatory modulation may require combination immunotherapy in which "cocktails" of empirical antibiotics

and antiinflammatory agents are used [141]. Conversely, a more sophisticated postreceptor therapeutic approach may be necessary, involving interruption of transcription, protein synthesis, and posttranslational events, thereby altering the cellular expression of cytokine release.

Fever in HIV-Infected Patients—John G. Bartlett, M.D.

Fever is common in HIV-infected patients. The initial acute retroviral infection, in fact, is characterized by a mononucleosis-like syndrome in which fever is almost invariably present. Fever during the subsequent course of HIV infection usually represents a superimposed complication of late-stage disease. The most common causes of such fever are opportunistic infections, neoplasms, and adverse drug reactions. Despite the frequency of fever during HIV infections, relatively little has been written on the subject, and many of the studies to date have been described only in abstract form.

An acute febrile illness of 2–3 weeks' duration typically occurs 2–4 weeks after seroconversion in 50%–70% of HIV-infected patients. The syndrome is second in frequency only to influenza as a cause of acute febrile illness lasting >3 days in homosexual men [142]. Important clues to the presence of an acute HIV infection are associated high-risk behavior, fever lasting >1 week, weight loss, and typical symptoms such as aphthous ulcers. The diagnosis is established by demonstrating high-level HIV viremia (most often by detection of p24 antigenemia), combined with a negative or indeterminate HIV serology followed by seroconversion.

AIDS-defining diagnoses in cases reported to the Centers for Disease Control and Prevention in 1994 are summarized in table 6 [143]. The most common causes of fever of unknown origin (FUO) in HIV-infected patients are *Pneumocystis carinii* pneumonia (PCP), tuberculosis, cytomegalovirus disease, dis-

seminated disease due to *Mycobacterium avium* complex (MAC), toxoplasmosis, cryptococcosis, and non-Hodgkin's lymphoma. Other pathogens that reflect endemic disease include malaria, leishmaniasis, *Penicillium marneffeii* infection, histoplasmosis, and coccidioidomycosis [144–153].

Tuberculosis often occurs when CD4 cell counts fall below 200/mm³; most other conditions listed develop in the face of median CD4 cell counts of 20–50/mm³. Two exceptions are seen in HIV-infected patients with concurrent human T-cell leukemia virus-1 infection and splenectomy, both of which are associated with deceptively high CD4 cell counts. The most common missed diagnoses according to autopsy studies are disseminated cytomegalovirus infections and disseminated MAC infections [144, 145].

Approximately 20% of AIDS patients receiving trimethoprim-sulfamethoxazole (TMP-SMZ) develop fever, but this is almost invariably accompanied by a typical rash or pruritus. Clinical clues and preferred diagnostic tests for the most common infections are summarized in table 7. Less frequent causes of FUO include sinusitis; salmonellosis; pyomyositis; infection with *Nocardia* species, *Mycobacterium kansasii*, *Mycobacterium genavense*, *Mycobacterium haemophilium*, and other mycobacteria; herpes simplex; aspergillosis; and Kaposi's sarcoma with B-form symptoms.

An estimated 75%–85% of patients with HIV infections develop PCP, unless prophylaxis is administered, making PCP the most common initial AIDS-defining diagnosis [143] and the most frequent identifiable cause of death in all autopsy-based studies. Virtually all patients with PCP have respiratory symptoms and manifest an FUO only when there is an atypical presentation or a negative chest roentgenogram; negative roentgenograms are seen in up to 40% of cases [154].

Tuberculosis is a frequent cause of FUO among HIV-infected patients because it is common and because most patients have atypical presentations with negative chest radiographs (up to 40%), negative PPD tests (most patients with CD4 cell counts <200/mm³), and negative smears of respiratory secretions for acid-fast bacilli (~50%) [155, 156]. Disseminated cytomegalovirus infection is a complication of late-stage disease characterized by a CD4 cell count that is usually <50/mm³. Retinitis accounts for 60%–75% of such cases.

Disseminated MAC infection is the most common cause of FUO in patients with advanced HIV infection, in large part reflecting the 5–12 days required for growth of the microbe in blood cultures and the lack of focal findings in many patients. Night sweats, diarrhea, abdominal pain, weight loss, hepatosplenomegaly, anemia (hematocrit, <25%) and an elevated serum alkaline phosphatase level are frequent manifestations of the illness [157–159].

Kaposi's sarcoma, non-Hodgkin's lymphoma, and primary CNS lymphoma are the most common malignant neoplasms associated with HIV infection. Kaposi's sarcoma is readily recognized by its characteristic skin lesions and is usually not associated with fever or other B-form symptoms unless visceral

Table 6. Relative frequency of AIDS-defining diagnoses for cases of AIDS reported to the Centers for Disease Control and Prevention in 1994.

AIDS-defining diagnosis	No. (%) of diagnoses (n = 57, 270)
<i>P. carinii</i> pneumonia*	15,187 (27)
Wasting	7,636 (13)
Esophageal candidiasis	5,793 (10)
Tuberculosis*	4,179 (7)
Cytomegalovirus disease*	3,677 (6)
Kaposi's sarcoma	3,467 (4)
<i>M. avium</i> complex infection (disseminated)	2,478 (4)
Recurrent pneumonia	2,252 (4)
Herpes simplex (chronic)*	2,137 (4)
HIV dementia	1,881 (4)
Toxoplasmosis*	1,881 (3)
Cryptococcosis*	1,816 (3)

* Associated with fever.

Table 7. Common causes of fever of unknown origin in patients infected with HIV.

Diagnosis	Clues	Diagnostic test
PCP	Virtually always, respiratory symptoms (cough, fever, dyspnea); LDH, elevated (90%); chest radiograph, normal (15%–30%); partial pressure of O ₂ , <90 mm Hg; CD4, <200	Induced sputum (sensitivity, 60%) or bronchoscopy (sensitivity, >95%); response to treatment
Tuberculosis	Atypical presentation with increased rates of primary progressive form, extrapulmonary-meningeal form, and lymphadenopathy; median CD4, 200–300; most AFB in sputum are tuberculous; LDH, elevated in extrapulmonary tuberculosis	Acid-fast smear (for presence of AFB in respiratory secretions—60% sensitive); culture
Cytomegalovirus disease	Constitutional symptoms: fever, weight loss ± organ involvement (eye, esophagus, or colon), and peripheral or CNS symptoms; CD4, <50	Ophthalmologic examination; biopsy of tissue to demonstrate pathogen; quantitative PCR for cytomegalovirus (?)
MAC infection	Constitutional symptoms: fever, weight loss ± diarrhea, and anemia + increased alkaline phosphatase level; CD4, <50	Blood culture (90% sensitive, but requires 5–12 d)
Cryptococcosis	Usually CNS symptoms ± pulmonary infiltrate and skin lesions; CD4, <100	Serum cryptococcal antigen (sensitivity, 95%)
Toxoplasmosis	Usually CNS symptoms ± focal neurological signs; CD4, <100	MRI for typical lesion; response to empirical treatment within 1 w; toxoplasmosis serology for IgG (sensitivity, 85%–90%)
Lymphoma	Usually extranodal visceral involvement; response to naproxen challenge (complete and sustained lysis of fever within 24 h); CD4, <200; LDH, elevated	Biopsy

NOTE. AFB = acid-fast bacilli; CD4 = CD4 cell count (/mm³); LDH = lactate dehydrogenase level.

involvement has occurred [160]. Non-Hodgkin's lymphoma may be seen in relatively early-stage HIV infection and is usually an aggressive, high-grade B-cell lymphoma with extensive visceral involvement and B-form symptoms, including fever [161, 162]. In some patients, the fever responds rapidly to naproxen challenge, which may serve as an important diagnostic clue [163]. CNS lymphoma is usually seen only in late-stage HIV disease and is infrequently associated with fever [161].

Patients with HIV infections appear to be uniquely susceptible to adverse drug reactions, especially late in the course of their disease [164]. The frequency of fever among TMP-SMZ recipients is ~20% [165]. Other drugs used for HIV-infected patients that seem to be associated with high rates of adverse reactions (including fever) are dapsone, clindamycin, β -lactam antibiotics, phenytoin, carbamazepine, thalidomide, and pentamidine [165, 166]. Nucleoside analogs have rarely been implicated as causes of fever [167]. Patients with febrile reactions (except for those due to pentamidine and AZT) almost always have an associated rash [164–167].

Injection drug use has been identified in 41% of recently reported cases of AIDS in the United States and is a risk factor having a differential diagnosis of fever independent of that associated with the HIV infection itself [168, 169]. A recent review of 121 febrile hospitalized injection-drug users showed 51% had bacteremia; *Staphylococcus aureus* accounted for 32 of the 61 cases (52%) and 15 of these patients had endocarditis (13% overall) [170].

Guidelines for the evaluation of fever in patients with HIV infections are based on signs, symptoms, and stage of disease. Patients with CD4 cell counts of >500/mm³ should be evalu-

ated as immunocompetent hosts. The following recommendations apply to patients with significant impairment of cell-mediated immunity, as indicated by CD4 cell counts of <200/mm³.

Lactate dehydrogenase levels, while nonspecific, are usually elevated in PCP, extrapulmonary tuberculosis, disseminated MAC infections, and lymphoma. Whereas serological tests for toxoplasmosis are useful in evaluating fever in patients with AIDS, the sensitivity of serological tests for coccidioidomycosis and histoplasmosis is low. Serum cryptococcal and histoplasmal antigen assays show sensitivities exceeding 85% [171, 172]. The PPD skin test has a sensitivity of 10%–70%, depending on the stage of HIV infection.

Anergy screening is no longer advocated for HIV-infected patients. With regard to scans, CT of the abdomen and chest is helpful diagnostically in 20%–50% of febrile patients with AIDS [173, 174]. Gallium scans are sensitive but not very specific and are most useful for patients with Kaposi's sarcoma of the lung, in whom gallium uptake is poor. Indium-labeled leukocyte scintigraphy is more sensitive than gallium scintigraphy in AIDS patients with FUO [175].

Liver biopsy has a high diagnostic yield, especially when the serum alkaline phosphatase level is elevated. With alkaline phosphatase levels of 2.5 times the upper limit of normal, liver biopsy is reported to have a diagnostic yield as high as 75% [176]. Prior to performing such a biopsy, however, it is important to exclude diagnoses such as viral hepatitis, adverse drug reactions, and HIV-associated cholangiopathy. The most common diagnosis made via liver biopsy is mycobacterial infection.

Bone marrow biopsies generally have lower diagnostic yields than do liver biopsies [177]. The utility of a lumbar

puncture in the evaluation of FUO in HIV-infected patients without symptoms or signs of CNS disease is not known. Fine-needle aspiration of lymph nodes is rapid, safe, and especially useful in detecting mycobacterial infections and lymphoma [178].

In summary, FUO is relatively common in patients with HIV infection, especially in those with late-stage disease. The differential diagnosis and diagnostic evaluation for such patients are in many ways unique [179]. Most studies indicate that an etiologic diagnosis can be established for 70%–90% of AIDS patients with FUO. Opportunistic infections account for the great majority of such fevers. Fever rarely resolves spontaneously in undiagnosed cases.

Concluding Remarks—Philip A. Mackowiak, M.D.

To fully appreciate the clinical implications of fever, one must take a broad view of the physiological response. Fever is more than an elevation in core temperature. As amply documented in the symposium summarized here, it is a complex physiological response, also involving generation of a host of cytokines and acute-phase reactants (although apparently not invariably) and activation of numerous physiological, endocrinologic, and immunologic systems.

As such, fever cannot be equated with hyperthermia. Experimental models of “fever,” including heat stroke and malignant hyperthermia, in which body temperature is elevated either by external means or by agents that markedly increase heat production via uncoupling of oxidative phosphorylation, must be recognized as having limited value in the study of this physiological response.

Only if we view the febrile response in its entirety can we begin to explain the apparent paradox inherent in reports demonstrating beneficial effects of therapy with both pyrogenic cytokines and their antagonists, and through such understanding take maximum advantage of the response to alleviate the burden of some of the most refractory diseases of our age.

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