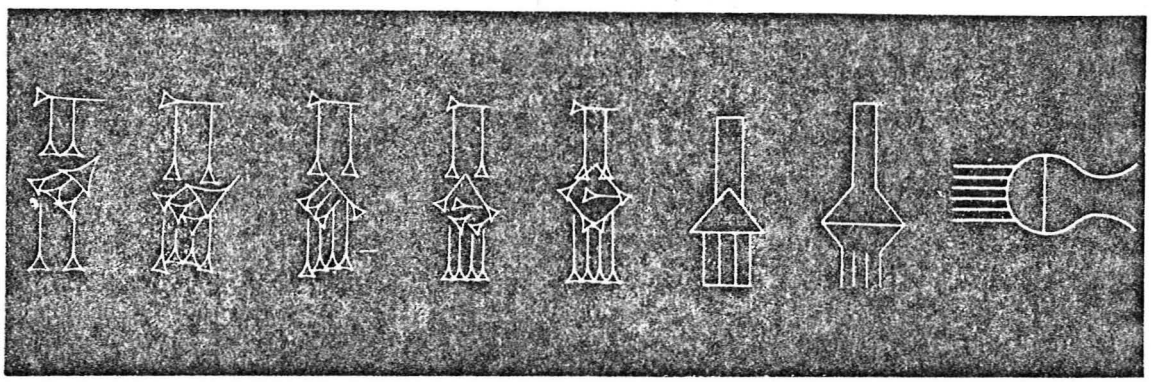
MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL



TELEOLOGICAL ENIGMA : FEVER

September 20, 1979

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A recent point prevalence survey of antipyretic use at the Dallas V.A. Medical Center (Table 1) revealed a high rate of antipyretic use by our housestaff in hospitalized patients. Although many of the patients for whom these drugs (primarily aspirin and tylenol) had been prescribed were receiving them because of their analgesic or anti-coagulant effect, 7% of the patients on the medical and surgical services were receiving these agents specifically to suppress fever. Furthermore, 15% of the patients were receiving concomitant antipyretic and antibacterial therapy, suggesting either a concern among the housestaff that fever might have a deleterious effect on the outcome of infections, or, at the very least, a conviction that suppression of fever in infected patients is of no consequence relative to the course of their infections. Surprisingly, the surgical housestaff and the medical housestaff appeared to be equally eager to suppress fever in the setting of infection.

TABLE 1. Point prevalence survey of antipyretic use at the Dallas V.A. Medical Center, August 17, 1979

		Pts. Receiving Antipyretics*		
Service	Total pts. examined	Total	For suppression of fever	With concomitant antibiotics
Medical	214	108(50)	18(8)	31(14)
Surgical	178	119(67)	11(6)	27(15)
Combined	392	227(58)	29(7)	58(15)

* No. (% of Total)

Like our own housestaff, clinicians dating to antiquity have been preoccupied with the problem of the clinical significance and treatment of fever. There has been both a tendency among them to assume that because fever occurs in the setting of disease, it is itself detrimental to the host, and, conversely, that because it is such a universal response to infection, it represents an adaptive response of higher animals having some survival value. Incredibly, in spite of voluminous literature promoting one view or the other over the years, only recently has the problem of the teliological significance of fever been subjected to careful scientific scrutiny.

In this Grand Rounds, I will attempt to review the current status of

available data relating to the basic question of whether fever is an adaptive mechanism of higher animals or simply an unavoidable by-product of inflammation exerting either no independent effect or even a deleterious effect on the outcome of infection. Since two recently published reviews of fever (1,2) have already catalogued existing data relating to the pathogenesis of fever and its effect on host defenses, I will review these areas briefly for the sake of completeness, and will devote the bulk of my discussion to investigations relating to the effects of fever on pathogenic microorganisms. In doing so I will review preliminary results of related experiments conducted at our own institution and will attempt to point out some of the difficulties encountered in attempts to extrapolate from these studies and the work of others to clinical situations.

PATHOGENETIC CONSIDERATIONS

The current status of our understanding of the pathogenesis of fever is summarized in Figure 1 (3). As indicated, the febrile response to virtually all infections is mediated through the action of endogenous pyrogen on cells located in the pre-optic area of the anterior hypothalamus. Endogenous pyrogen has been characterized as a protein of low molecular weight (4). It is generally produced and then released by phagocytic leukocytes (polymorphonuclear as well as mononuclear) in response to a diverse group of substances of which pathogenic microorganisms are the most familiar. However, some malignant tumors of macrophage origin appear to produce endogenous pyrogen spontaneously (3). The production of endogenous pyrogen by normal phagocytic leukocytes appears to involve derepression of the genome for endogenous pyrogen through an activation step, transcription of the genome into new messenger RNA, and subsequent translation into new protein. Once synthesis is completed, the molecule is released without significant storage.

In addition to its role in mediating a rise in body temperature, endogenous pyrogen has also been shown to acutely reduce serum iron in experimental animals by causing a selective release of lactoferrin containing granules from circulating neutrophils (4). As suggested later in this review, this aspect of the febrile response may increase resistance to certain pathogenic bacteria by depriving them of needed iron.

In spite of intensive investigations into the mechanisms of fever in recent years, it is still not known whether endogenous pyrogen directly alters the activity of temperature-sensitive neurons in the pre-optic area of the anterior hypothalamus to induce them to elevate the body temperature "set point", or does so indirectly through some chemical mediator (2). Monoamine, sodium and calcium ions, prosta-

glandins and cyclic adenosine 3',5' monophosphate have each been examined as possible intermediaries between endogenous pyrogen and the anterior hypothalamus. However, neither these nor any other intermediary substances have been established as essential to the activity of endogenous pyrogen in inducing a febrile response in higher animals.

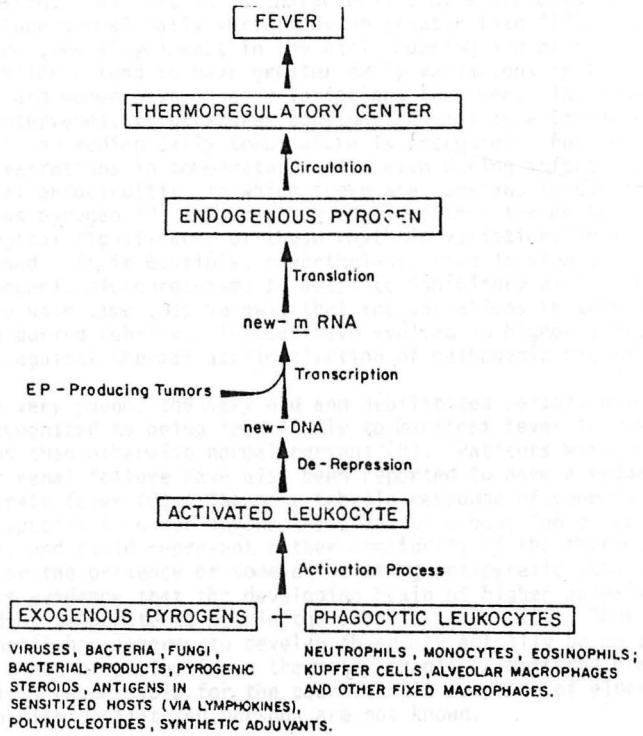


Figure 1. Proposed mechanism for the production of endogenous pyrogen. (Ref. 3)

The actual processes by which higher animals maintain normal body temperature or elevate temperature in response to pyrogens are complex and involve both physiologic and behavioral reactions (2). The primary physiologic reactions occurring in response to pyrogen include peripheral vasoconstriction (decreasing loss of body heat) and shivering (increasing production of body heat). Behavioral responses include such measures as application of warmer clothing by human subjects or

movement to a warmer environment by both man and lower animals (5). Thus the elevation in body temperature during fever is a regulated rise that is actively generated by the host and resistant to all but the most aggressive external efforts directed toward its reduction. These characteristics of the febrile response offer compelling evidence that it represents more than a passive by-product of the inflammatory response.

The normal body temperature of man and other warm-blooded animals is not constant. Rather, it is characterized by a circadian rhythm that may include normal daily variations of greater than ±1°C (6). Temperatures are generally lowest in the early morning and highest in the evening. Children tend to have greater daily variations in temperature than adults, and women have greater variations than men. Interestingly, when fever intervenes, temperatures continue to vary in a circadian fashion, although the median daily temperature is increased. Furthermore, circadian variations in temperature occur even during infections such as bacterial endocarditis, in which there are constant levels of circulating exogenous pyrogen (7). To my knowledge, neither the mechanisms nor the teliological significance of these rhythmic variations in fever have been determined. It is possible, nevertheless, that in view of the capacity of pathogenic microorganisms to adapt to inhibitory elevations in temperature with time (see below), that the variations in temperature occurring during febrile illnesses have evolved in higher animals as a defense against thermal acclimatization of pathogenic microorganisms.

The very young, the very old and debilitated persons have classically been recognized as being less likely to manifest fever in response to infections than otherwise normal persons (8). Patients with underlying chronic renal failure have also been reported to have a reduced ability to generate fever (9). The poor febrile response of neonatal homeotherms appears to occur beyond the stage of production of endogenous pyrogen, and could represent either immaturity of the thermoregulatory center or the presence of some circulating antipyretic substance (10). There is evidence that the developing brain of higher animals may be damaged by temperatures within the febrile range (11). Thus the "failure" of neonatal homeotherms to develop fever may actually be an adaptive response aimed at protecting a thermally fragile (immature) brain. The mechanisms responsible for the poor febrile response of elderly, uremic or otherwise debilitated persons are not known.

Thus fever is a complex process which is actively maintained by most higher animals in response to infection by a wide variety of pathogenic microorganisms. It is not synonymous with hyperthermia since it involves more than a simple elevation of the body temperature. Consequently, many studies of fever, which have involved elevation of body temperature through external means, or have produced continuous elevations in body temperature in experimental animals and have ignored the rhythmic variations in temperature seen in most febrile illnesses are of questionable relevance to the process of fever in man. Likewise, data from those

students of fever who have examined experimentally induced hypothermia on the assumption that it will have an opposite effect on the host may not have provided any true insight into the nature of fever. Unfortunately, much of the data supporting our current concepts of fever have been accrued through studies incorporating these flaws in experimental design.

DIAGNOSTIC CONSIDERATIONS

Fever is an almost universal sign of infection and is also common in non-infectious disorders. As such, the temperature curve may be of value to the clinician both in alerting him to the presence of disease, and serving as a useful parameter by which progress of the disease or response to therapy may be measured. These assets alone would seem to dictate against indiscriminate suppression of fever in the absence of convincing evidence of a detrimental effect of fever on the course of these disorders.

The study of fever patterns has been an obsession of clinicians since the time of Hippocrates (12). In fact, until the very recent past, clinicians could do little more with the major diseases of mankind than describe their characteristic fever patterns and note changes occurring in these as a result of available therapeutic interventions. The preoccupation of this century's clinicians with patterns of fever is typified by the first edition of Sir William Osler's The Principles and Practice of Medicine, which devoted 12 of 19 charts (most of the few illustrations present in the textbook) to temperature graphs of patients with various disorders (13).

In fact, throughout the history of medicine considerable effort has been directed toward attempts to codify patterns of fever in the hope that characteristic configurations of the febrile response might be gleaned from clinical records that would enable the clinician to identify specific diseases (14). This kind of exercise has enabled students of physical diagnosis to group fever patterns into such familiar categories as "continuous," remittent," intermittent," and "recurring," and thus create a facade of order out of the chaos of an almost unlimited number of febrile illnesses. Unfortunately, even patterns of such traditional significance as the Pel-Epstein fever of Hodgkin's disease (15), the reversal of the diurnal variation seen in miliary tuberculosis (8), and the pulse-temperature dissociation of typhoid fever (16) are now recognized as common to many different disorders. Thus, many different types of diseases may have similar or identical patterns of fever, and, with the possible exception of those patterns seen in tertian and quartan malaria, clinicians derive little

help from a simple inspection of the temperature chart in narrowing lists of differential diagnoses (12).

The height of the febrile response is no more helpful in identifying given diseases or groups of diseases than is the pattern of fever (17). In general, if a disorder is capable of producing fever, it is capable of producing high fever. Furthermore, the magnitude of the febrile response is of little help in differentiating infection from thermoregulatory failure as a cause for the fever.

In spite of these shortcomings in specificity as a diagnostic marker, fever may be one of the most sensitive indicators of disease in certain circumstances. Perhaps nowhere is this characteristic better illustrated than in the case of the patient with fever of unknown origin. By definition, this is an illness characterized by persistent fever (and this is frequently the only symptom of disease) that remains undiagnosed in spite of at least a week of careful study in a hospital. Published experiences with fever of unknown origin indicate that the cause is most often an unusual presentation of a common disorder (Table 2). Causes of fever of unknown origin in children (19,22) are similar to those in adults (18,20,21) except that in pediatric series, juvenile rheumatoid arthritis and chronic viral infections are much more common than in adult series (18,20,21). A constant feature of both pediatric and adult series is the relatively large number of patients with underlying hematologic malignancies, a finding no doubt relating to observations that malignant cells of macrophage origin may produce endogenous pyrogen spontaneously (3).

FEVER AND HOST DEFENSES

The function of most of the known components of the immunologic network of higher animals has been studied *in vitro* at various temperatures within the physiological range (1). In some cases, temperatures within the range encountered in febrile illnesses in man have produced enhanced function of these components, whereas in other instances febrile temperatures have either had no apparent effect, or have actually diminished the activity of the immunologic responses.

The polymorphonuclear leukocyte has been intensively studied in this regard. *In vitro* studies of polymorphonuclear leukocyte motility have provided conflicting reports of the effect of variations in temperature within the physiologic range on this phenomenon. Phelps and Stanislaw (23) found that decreasing the incubation temperature from 37.7 to 33.9C resulted in a 50% reduction in motility, but found essentially no difference in the motility of human polymorphonuclear leukocytes between 37 and 42C. Although their findings appear to have

TABLE 2. Causes of Fever of Unknown Origin in 154 Pediatric* and 234 Adult Patients in 5 Previously Reported Series

Diagnosis	Petersdorf & Beeson (18)	Pizzo* et al (19)	Gleckman et al (20)	Howard et al (21)	Lohr & Hendley (22)	Combined Series
Infections	38	54	7	37	17	153(39%)
Endocarditis	5	3		9	1	18(5%)
Abdominal Abcess	4	1	2	9	1	17(4%)
Hepatobiliary	7	1	1	7	1	17(4%)
Urinary	3	4		4	3	14(4%)
Mycobacterial	11	1	2	3	3	20(5%)
Brucellosis	1			1		2(1%)
Bone/Joint	1	2	2	1	1	7(2%)
Meningitis (Bacterial)		3		1	1	5(1%)
Viral		20			3	23(6%)
Misc.	6	19		2	3	30(8%)
Neoplastic	19	6	3	31	7	63(17%)
Lymphoma/Leukemia	8	6	3	23	6	46(12%)
Carcinoma	7			6		13(3%)
Misc.	4			2	1	7(2%)
Collagen/Vasc.	15	20	3	19	11	68(18%)
S.L.E.	5	3		3		11(3%)
Rheumatoid Arthritis		10	1	3	7	21(5%)
Misc.	10	7	2	13	4	36(9%)
Miscellaneous	28	20	21	13	19	101(26%)
Pulmonary Emboli	3		3			6(2%)
Sarcoidosis	2					2(1%)
Hypersensitivity	4			3	2	9(2%)
Factitious	3		1		2	6(2%)
Other	9	8	5	9	5	36(9%)
No diagnosis	7	12	12	1	10	42(11%)
TOTAL	100	100	34	100	54	388(100%)

been corroborated by those of Austin and Truant (24), who noted similar chemotactic activity of polymorphonuclear leukocytes at 37 and 40C, these investigators found a marked reduction in chemotactic activity by polymorphonuclear leukocytes in the presence of two common antipyretic agents, sodium salicylate and phenacetin (Figure 2).

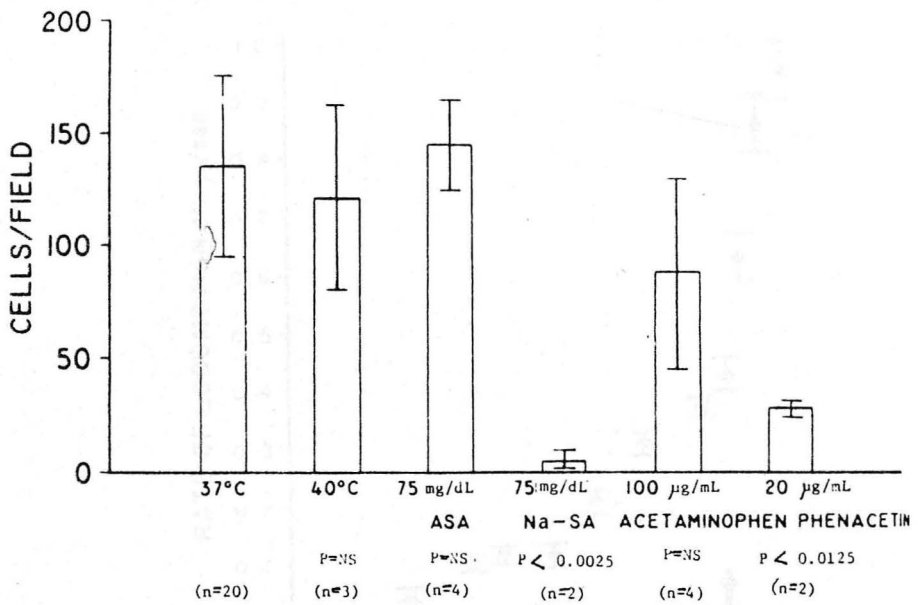


Figure 2. Polymorphonuclear leukocyte chemotactic activity. Ambient temperature of 40C and acetylsalicylic acid and acetaminophen did not adversely affect PMNL migration, whereas sodium salicylate and phenacetin did. Results represent mean ± standard deviation. Na-SA = sodium salicylate; NS = not significant. (Ref. 24).

Nahas, et al (25) and Bryant, et al (26) have obtained data that are in direct conflict with those cited above. Both groups of investigators observed marked enhancement in polymorphonuclear leukocyte mo-

tility as incubation temperature was increased within the physiologic range. Maximum activity was observed at 40-42C. Figure 3 illustrates the findings of Nahas, et al (25). No explanation is readily apparent for the discrepancy between the results of these investigators and those of Phelps and Stanislaw (23) and Austin and Truant (24). Considering the data from all of these investigators, it would appear that temperatures below 37C are associated with depressed polymorphonuclear leukocyte motility, whereas those above 37C (within the physiologic range) are associated with levels of motility that are at least as great and perhaps greater than those occurring at 37C.

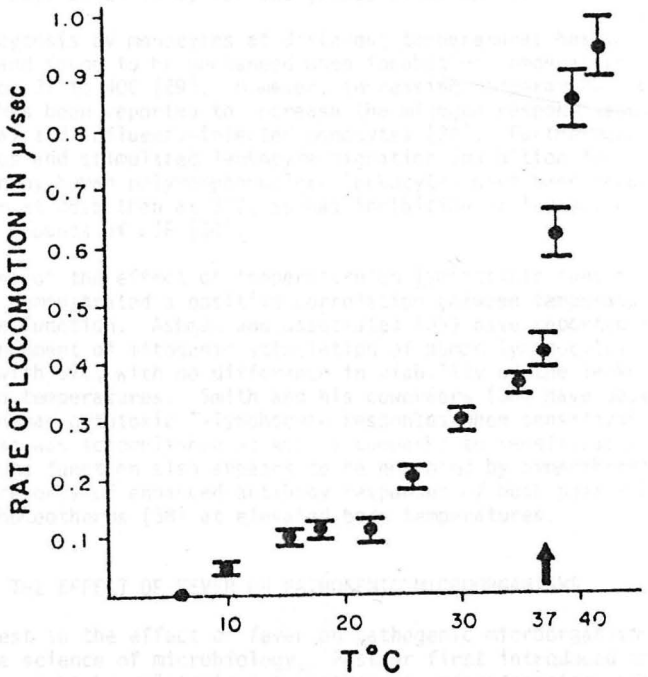


Figure 3. Rate of locomotion of human polymorphonuclear neutrophils in function of temperature (pH 7.43). (Ref. 25).

Data relating to the effect of temperature on phagocytosis and bacterial killing by polymorphonuclear leukocytes are equally difficult to interpret. Positive correlations between temperature and phagocytosis and/or killing have been reported by three independent groups of

investigators (27-29). Other groups have also reported no differences in either phagocytosis or killing with change in temperature within the physiologic range (30,31). Peterson and coworkers (32) have even reported that at an incubation temperature of 41C polymorphonuclear phagocytosis may actually be depressed. Unfortunately, these investigators did not provide data on phagocytosis at incubation temperatures between 37 and 41C. Sebag, Reed and Williams (33) have demonstrated that relationships between temperature and the bactericidal capacity of polymorphonuclear leukocytes may vary depending on the species of bacteria being studied. These observations might explain some of the discrepancies between the data obtained by various groups cited above.

Phagocytosis by monocytes at different temperatures has also been examined and found to be unchanged when incubation temperature is raised from 37 to 40C (29). However, increasing temperature from 37 to 38.5C has been reported to increase the mitogen responsiveness of both normal and influenza-infected monocytes (34). Furthermore, both spontaneous and stimulated leukocyte migration inhibition factor (LIF) production by human polymorphonuclear leukocytes have been reported to be greater at 38.5 than at 37C, as has inhibition of leukocyte migration by givent amounts of LIF (34).

Studies of the effect of temperature on lymphocytic function generally have demonstrated a positive correlation between temperature and lymphocyte function. Ashman and associates (35) have reported significant enhancement of mitogenic stimulation of human lymphocytes at 39C compared with 37C, with no difference in viability of the leukocytes at the two temperatures. Smith and his coworkers (36) have observed enhanced human cytotoxic T-lymphocyte responses when sensitization of these cells was accomplished at 40C as compared to sensitization at 37C. B-lymphocyte function also appears to be enhanced by hyperthermia in light of reports of enhanced antibody responses of both poikilotherms (37) and homeotherms (38) at elevated body temperatures.

THE EFFECT OF FEVER ON PATHOGENIC MICROORGANISMS

Interest in the effect of fever on pathogenic microorganisms is as old as the science of microbiology. Pasteur first introduced the idea that fever might be deleterious to pathogenic microorganisms after demonstrating that the native immunity of the chicken to anthrax could be abbrogated by immersing it in cold water (39). His suggestion, however, that resistance to anthrax was due simply to the relatively high body temperature of the chicken, now appears to have been an oversimplification in view of Wagner's finding in later experiments that the anthrax bacillus could be grown in chicken blood at temperatures as high as 43C (40).

Like these early studies, many more recent studies have been plagued by difficulty in separating the effect of fever on host defenses from that on the pathogenic microorganisms themselves. Although *in vitro* studies have eliminated many of the confounding factors inherent in *in vivo* studies, these too may involve important variables other than temperature which may make interpretation difficult. The pH, oxygen content and chemical composition of the growth medium used to support microorganisms have each been shown to affect the temperature sensitivity of these microorganisms (41). Heat intolerance of many bacteria increases directly with O_2 content (Figure 4) but is indirectly correlated with pH. In view of these data, it is possible that the hyperemia, acidosis and hyperthermia that characterize areas of inflammation act synergistically to eliminate pathogenic microorganisms.

The temperature sensitivity of bacteria may also be affected by the growth phase of the organism at the time of challenge (41). In general, bacteria that are in the stationary growth phase exhibit increased heat resistance when grown at elevated temperatures. Unfortunately, neither these variables nor those mentioned earlier have been consistently controlled in *in vitro* experiments examining the effect of fever on microorganisms. Furthermore, relatively little of this work has been done by clinical microbiologists. Consequently, relatively few studies of the effect of hyperthermia on microorganisms have involved temperatures within the clinical range.

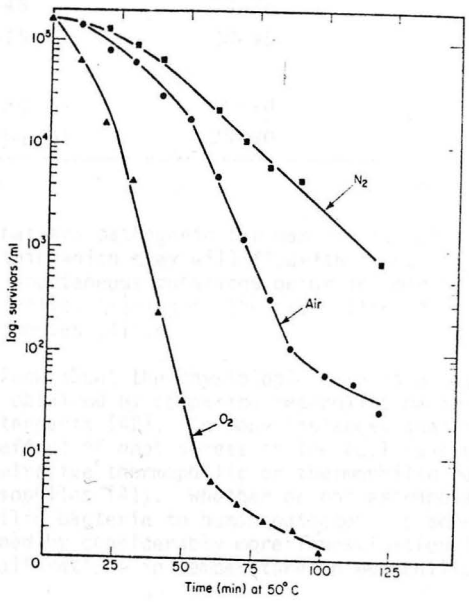


Figure 4. Effect of equilibration of heating menstruum to different gas mixtures on survival of *P. aeruginosa* at 50C in nutrient broth. ▲ Oxygen; ■ Nitrogen; ● 20% Oxygen and 80% Nitrogen. (Brown and Melling, unpublished results). (Ref. 41).

Bacteria: More is known of the effects of variation in temperature on bacteria than on any other group of microorganisms. Bacteria vary widely with respect to both the temperature at which they will grow optimally and the maximal and minimal temperatures at which growth will occur. In fact, they have been separated into arbitrary groups on the basis of these characteristics (Table 3).

TABLE 3. *Principal physiological categories of bacteria in terms of the relationship between growth rate and temperature*

	Temperature, °C		
Group	**Minimum**	**Optimum**	**Maximum**
Thermophiles	*40–45*	*55–75*	*60–80*
Mesophiles	*10–15*	*30–45*	*35–47*
Psychrophiles			
Obligate	*(−5)–(+5)*	*15–18*	*19–22*
Facultative	*(−5)–(+5)*	*25–30*	*30–35*

Almost all of the bacteria that are pathogenic for man are mesophiles, and the temperature range within which they will flourish is not easily altered (41). Nevertheless, spontaneous mutations occur in mesophilic bacteria at a rate of $\approx 1/10^6$ cells, leading to the production of thermophilic variants among these species (41).

A great deal of what we know about the physiologic effects of hyperthermia on bacteria has been obtained by comparing mesophilic bacteria with their thermophilic counterparts (42). In many instances quantitative data relating to the effect of heat stress on the cell have been obtained from studies of facultative thermophilic or thermophilic bacteria and extrapolated to mesophiles (41). Whether or not extrapolation of data obtained in thermophilic bacteria to human pathogens is appropriate, will have to be determined by considerably more investigation into the effect of physiological alterations in temperature on mesophilic bacteria.

Bacterial Growth: As early as the turn of this century, temperature was recognized as having a pronounced effect on bacterial growth rate. Figure 5 is from a paper published in 1908 and depicts the typical relationship between temperature and growth of a mesophilic bacterium (43). As illustrated, the growth rate increases rapidly as one approaches the

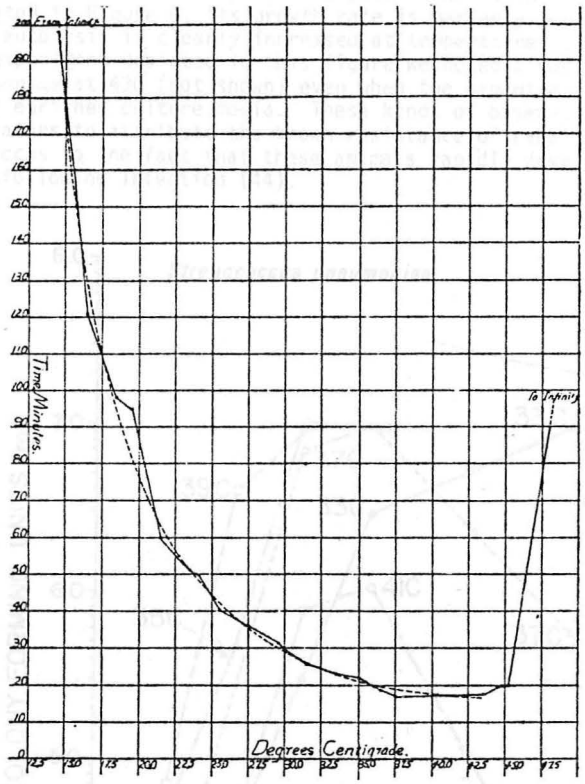


Figure 5. The growth rate of *E. coli* at different temperatures. The broken line approximates a curve plotted along the center of gravity of the points determined. (Ref. 43).

optimal temperature range from either the high or the low end of the viable temperature range. It is also clear from this graph that the growth rate of *E. coli* (and for that matter, most pathogenic bacteria), is maximal at ≈37C but varies relatively little within the physiological range (i.e., 33-41C). Although early investigators concluded from these findings that "no fever temperature in the human body can be high enough to directly inhibit the growth of pathogenic bacteria" (43), we now recognize that the growth of at least one bacterium patho-

genic for man may be profoundly affected by physiological variations in temperature. Type III *Streptococcus pneumoniae* is that pathogen. As illustrated in Figure 6, its growth rate is markedly reduced, and its rate of autolysis is clearly increased at temperatures of ≥41C. In fact, in the experiment depicted in this figure we noted a rapid destruction of *S. pneumoniae* at 43C (not shown) even when the organism was suspended in a highly enriched culture media. These kinds of observations led early investigators to attribute the known resistance of rabbits to Type III pneumococcus to the fact that these animals rapidly develop temperatures of ≥41C following infection (44).

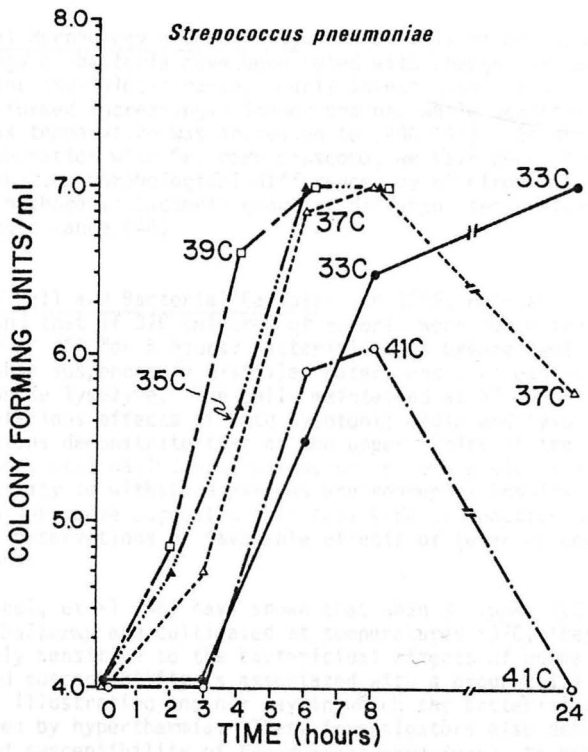


Figure 6. Standard growth curves of *S. pneumoniae* in Mueller-Hinton broth at 33, 35, 37, 39 and 41C.

In addition to affecting the growth rate of bacteria, temperature may also affect the *way* in which bacteria reproduce. That is, random cell division normally occurs in bacterial cultures, so that at any one time they contain a mixture of cells representing all phases of the division cycle (45). If, however, one subjects cultures to repeated alterations in temperature (e.g., alternating 37C and 25C), cell division will become synchronized, and at any point in time the majority of the cells in the culture will be in the same phase of the division cycle.

Bacterial Morphology and Motility: Relatively minor changes in gross morphology of bacteria have been noted with changes in temperature within the physiologic range. Early investigators found that some bacilli formed increasingly longer chains, while becoming less and less motile as temperature was increased to ≥40C (43). In our own studies in collaboration with Dr. Mary Lipscomb, we have been unable to demonstrate obvious morphological differences by electron microscopy between various pathogenic bacteria grown at different temperatures within the physiologic range (46).

The Cell Wall and Bacterial Capsule: In 1966, Hoffman and associates (47) found that if 37C cultures of *E. coli* were subjected to a temperature of 45C for 5 hours, bacterial cells became swollen and distorted when suspended in distilled water, and were easily destroyed by egg white lysozyme. The cells maintained at 37C were resistant to the deleterious effects of both hypotonic media and lysozyme. These observations demonstrate that at the upper limits of the viable temperature range, cell wall damage may occur in some bacteria and may decrease their ability to withstand various environmental insults. Hoffman and his coworkers have suggested that this kind of reaction might relate to clinical observations of favorable effects of fever on certain bacterial infections.

Muschel, et al (48) have shown that when *S. typhi* Ty2 or *Paracolobactrum ballerup* are cultivated at temperatures >37C, they become increasingly sensitive to the bactericidal effects of normal serum. The increased susceptibility is associated with a progressive loss of Vi antigen, illustrating another way in which the bacterial cell wall may be altered by hyperthermia. These investigators also demonstrated an increased susceptibility of *Pseudomonas aeruginosa* to normal serum and to antibiotics and detergent at 41C compared to 37C, but were unable to detect antigenic changes in pseudomonads subjected to 41C.

In our own institution, preliminary studies involving *Escherichia coli* 055 have demonstrated variations in the rate of accumulation of lipopolysaccharide in the supernatant of cultures grown at different

temperatures within the physiologic range (49). In these studies, the rate of accumulation of lipopolysaccharide was shown to increase directly with incubation temperature (Figure 7). Although the growth rate of this bacterium also varied somewhat with temperature (Figure 8), differences in growth were not equivalent to the differences in rate of accumulation of lipopolysaccharide at the temperatures studied. Whether

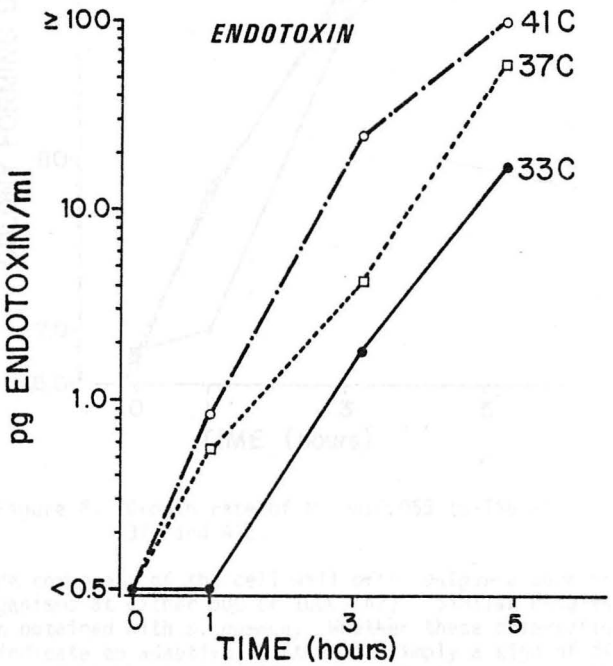


Figure 7. Rates of accumulation of lipopolysaccharide in the supernatant of cultures of *E. coli* 055 incubated in TSB at 33, 37, and 41C.

this increased rate of accumulation of lipopolysaccharide with increasing temperature represents increased production or simply increased release of lipopolysaccharide is not yet known.

Other investigators have noted a permanent loss of the lipopoly-

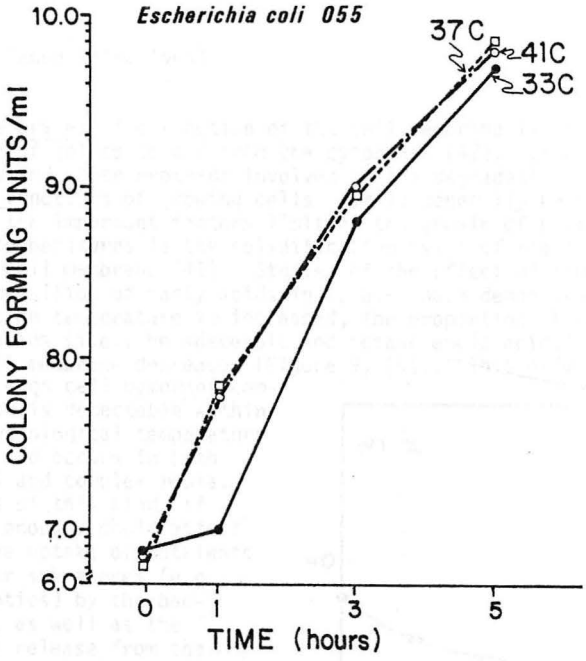


Figure 8. Growth rate of *E. coli* 055 in TSB at 33, 37, and 41C.

saccharide component of the cell wall of *P. vulgaris* upon heating these organisms at either 50C or 100C (42). Similar results have also been obtained with *S. aureus*. Whether these observations or our own indicate an adaptive reaction or simply a sign of distress on the part of the bacterium will require further studies to determine.

Relatively little is known of the effect of physiological variations in temperature on capsule production by pathogenic bacteria. It is known that *Y. pestis* will develop a loosely adherent antigen-containing envelope when cultivated at 37C, whereas this envelope is not present when the bacterium is grown at 28C (the body temperature of the flea) (50). This effect could represent an adaptive reaction on the part of the bacterium, since the envelope appears to increase resistance to phagocytosis. Unfortunately, to my knowledge, no one has examined the effect on capsule production of temperatures >37C (i.e., those commonly encountered in patients with

acute plague infections).

Cell Membrane: The function of the cell membrane is to control the passage of solute to and from the cytoplasm (42). It contains many enzymes and other proteins involved in the degradative and biosynthetic functions of growing cells. It is generally believed that one of the important factors limiting the growth of bacteria at elevated temperatures is the solidification point of the lipids making up the cell membrane (41). Studies of the effect of temperature on the composition of fatty acids in *E. coli* have demonstrated that as incubation temperature is increased, the proportion of unsaturated fatty acids (i.e., hexadecenoic and octadecenoic acids) making up the cell membrane decreases (Figure 9) (51). This effect of temperature on cell membrane composition is detectable within the physiological temperature range, and occurs in both minimal and complex media. Changes of this kind, if severe enough, could affect both the uptake of nutrients or other substances (e.g., antibiotics) by the bacterium, as well as the natural release from the cell of materials contained within the cytoplasm.

In 1966, Iandolo and Ordal demonstrated a temporary loss of salt tolerance by *Staphylococcus aureus* after it had been subjected to a temperature of 55C for 15 minutes (52). They hypothesized that this manifestation of thermal injury was due to changes in the cell membrane induced by the elevated temperature. Whether these or similar changes occur in man at the temperatures normally generated in response to pyogenic infections is not yet known.

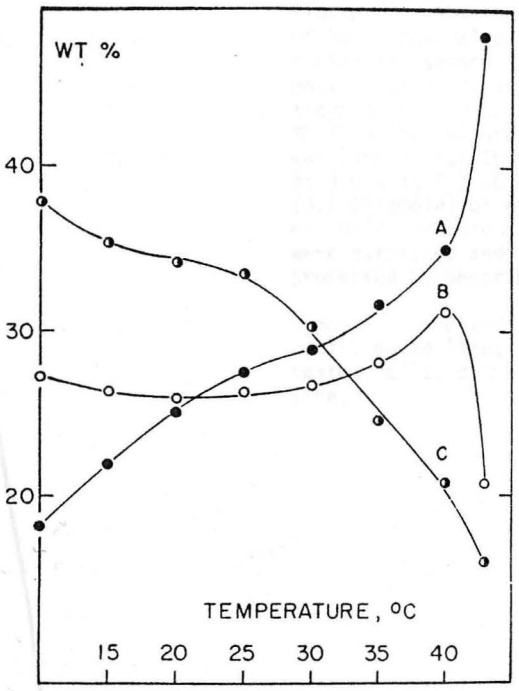


Figure 9. *Effect of growth temperature on the fatty acid composition of Escherichia coli ML30 harvested during exponential growth in glucose-minimal medium. Per cent by weight of the total fatty acids is calculated as methyl esters, neglecting lauric acid.* **A**, *palmitic acid;* **B**, *sum of hexadecenoic acid and methylene hexadecanoic acid;* **C**, *octadecenoic acid*

Bacterial Metabolism: The primary lethal event in the thermal inactivation of mesophilic bacteria may be the production of single-stranded breakes in DNA (42). These heat-induced breaks which are similar to those produced by ionizing radiation are readily apparent in cultures of *E. coli* that have been subjected to 52C for as short a time as a few minutes. Unfortunately, insufficient data are available to answer the question of whether exposure to temperatures within the physiological range leads to sublethal alterations of bacterial DNA that limit the organisms' invasive potential.

It is, however, well established that at temperatures between 30 and 47C, the rate of RNA degradation in some bacteria increases linearly with temperature (53). Furthermore, it is the 30S subunits of bacterial ribosomes that appear to be most sensitive to thermal destruction (Figure 10)(42,54,55). This phenomenon could be responsible for the increased rate of destruction of some bacteria by ribosomally active antibiotics at elevated temperatures (see below).

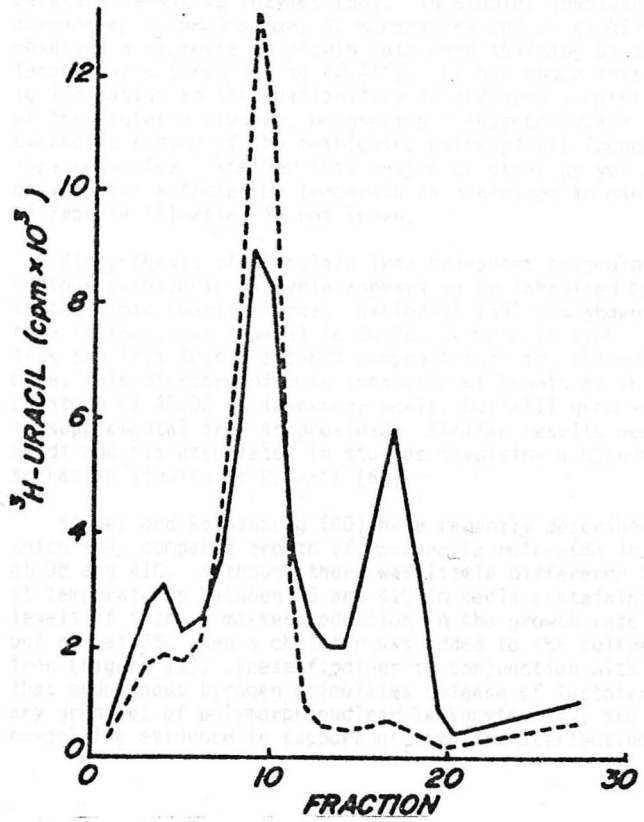


Figure 10. Absence of 30S ribosomal particles in (second peak) heated preparations of *S. aureus* MF-31. The culture was labeled for 16 hrs at 37C with 0.1 μCi/ml (3.1 Ci/nmole) of uracil-6-^{3}H. Ribosomes were extracted and processed as described.

Symbols: unheated cells, solid line; heated cells, dashed line.

Patterson and Gillespie (56) have shown that as one increases the incubation temperature of cultures of *E. coli* from 30 to 44C, a transient decrease occurs in the rate of uridine incorporation, amino acid incorporation, and increase in optical density. Although degradation of RNA can be demonstrated as temperature is increased, degradation of RNA precedes the loss of viability of cells. Hence, the primary effect on susceptible bacteria of temperature elevations of this magnitude appears to be on molecules required to initiate protein synthesis, while the effect on RNA synthesis appears to be secondary.

Other studies of the effect of sublethal heat (i.e., 52C) on the metabolic activity of pathogenic bacteria have shown both a general decrease in catabolic activity of these bacteria, and reduced production of selected end-products associated with the metabolism of glucose (57). Data recently published by E.Z. Ron suggests that these alterations in metabolic activity might be due to inactivation of temperature-sensitive enzymes (58). In studies involving *E. coli, A. aerogenes, K. pneumoniae, S. marcescens* and *S. typhimurium*, Ron has observed a decrease in growth rate when shifting bacteria to elevated temperatures (from 37C to 42-44C). He has shown this effect to be due to limitation in the availability of endogenous methionine. In three of the bacteria studied, homoserine transsuccinylase (the first biosynthetic enzyme of the methionine pathway) was found to be temperature-sensitive. Whether this enzyme or other as yet unidentified vital enzymes are affected by temperatures generated in man during the course of febrile illnesses is not known.

Biosynthesis of phenolate iron transport compounds (siderophores by various pathogenic bacteria appears to be inhibited by temperatures within the human febrile range. Garibaldi (59) has shown that as temperature is increased from 31 to 36.9C, *Salmonella typhimurium* Tm-1 excretes less and less iron transport compound into its culture medium. Furthermore, this microorganism is incapable of growth at an incubation temperature of 40.3C in iron-poor media, but will grow at this temperature if supplemental iron is provided. Similar results were obtained by Garibaldi and his associates in studies involving a pseudomonad, and by Kochan in studies of *E. coli* (60).

Kluger and Rothenberg (60) have recently described experiments in which they compared growth of *Pasturella multocida* in iron-poor media at 38 and 41C. Although there was little difference in its growth rate at temperatures between 38 and 41C in media containing physiological levels of iron, a marked reduction in the growth rate occurred at 41C but not at 38C when a chelator was added to the culture media to reduce iron (Figure 11). These findings in conjunction with recent evidence that endogenous pyrogen stimulates release of lactoferrin from the secondary granules of polymorphonuclear leukocytes (4), are some of the most compelling evidence in support of theories attributing an adaptive function

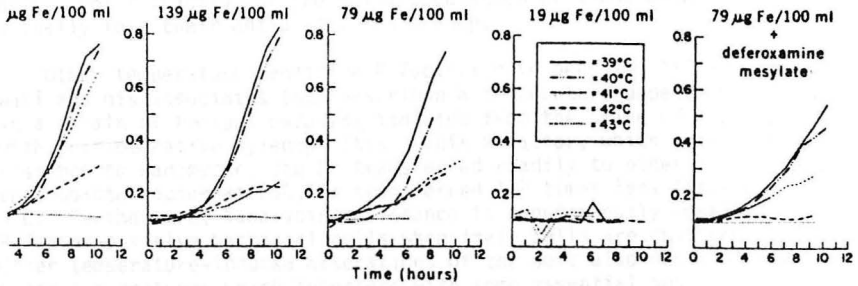


Figure 11. Growth of *Pasturella multocida* at temperatures of 39 to 43C and in iron concentrations of 19 to 266 µg per 100 ml of growth medium. At an iron concentration corresponding to the normal plasma concentrations of iron in uninfected rabbits (266 µg per 100 ml), the bacteria grew well at 39, 40, and 41C. When the bacteria were grown in a medium containing concentrations of iron corresponding to that which occurs in rabbits during infection (139 or 79 µg per 100 ml), the growth of the bacteria was not inhibited at the afebrile temperatures of 39 or 40C, but was depressed at the febrile temperature of 41C.

to fever. These data illustrate an effect of the febrile response of higher animals both on increasing the host's ability to withhold iron from potential pathogenic bacteria, and limiting the ability of the same pathogens to sequester iron that is available.

Virulence Factors: Alterations in the phenotypic expression of some bacterial proteins may be conditional in that these proteins express a mutant phenotype only under appropriate conditions (61). Temperature is a condition that may markedly affect the phenotypic expression of a few proteins controlling bacterial virulence factors. These conditional mutations involve a structural alteration of the protein as a result of an amino acid substitution that exerts its effect only within a defined temperature range.

Asheshov has shown that growth at temperatures near the upper end of the human physiological range can induce a loss of antibiotic resistance in *Staphylococcus aureus* (62). In his studies, 12 of 50 penicillin-resistant strains of *S. aureus* demonstrated a loss of the ability to produce penicillinase when subcultured at 43-44C for 5½ hours. Three of these strains also showed increased sensitivity to tetracycline after exposure to the elevated temperature. Unfortunately,

only a small fraction of the total population of transformed strains actually lost their antibiotic resistance.

Other temperature-sensitive R-factors have been identified. Terawaki and his associates (63) described a temperature-dependent R-factor in a strain of *Proteus vulgaris* isolated from the urine of a patient with post-operative pylenephritis. This R-factor, which transfers resistance to kanamycin, can be transferred readily to other strains of Enterobacteriaciae at 25C, is transferred 10^5 times less frequently at 37C. Furthermore, kanamycin-resistance is spontaneously reversed in R-factor-positive bacterial cells when these cells are cultured at 42C. Other temperature-induced alterations of the cell also occur at elevated temperatures which interfere with some essential host function, causing both a steady decline in the rate of precursor incorporation per cell particle into deoxyribonucleic acid, ribonucleic acid and protein, and a heightened sensitivity to both kanamycin and actinomycin D (64). Although other thermosensitive R-factors have been identified (65), they have yet to be shown to be of major clinical importance.

The activities of a number of bacterial toxins have been shown to be temperature-dependent. Of these toxins, exotoxin A of *Pseudomonas aeruginosa* may be of some clinical importance, since it inhibits mammalian protein synthesis by the same mechanism as diphtheria toxin (66). Exotoxin A is rapidly inactivated by heating at 45-60C. Similar results have been observed with the hemolysin of *V. parahaemolyticus* and with Staphylococcus α-toxin.

Listeria monocytogenes becomes increasingly virulent for mice when cultured at 4C (67). It has been suggested that its relatively low virulence for man could relate to a loss of virulence factors resulting from exposure to the considerably higher temperature of the human body. However, a specific temperature-sensitive virulence factor(s) has not yet been identified in this bacterium.

Antibiotic Sensitivity: In 1946 Johnson and Lewin reported that the inhibitory action of quinine on *E. coli* increased gradually as incubation temperature of the reaction mixture was increased from 18 to 37C and increased very strikingly between 37 and 40.9C (68). Since that time numerous investigators have examined the effect of temperature on the activity of antibacterial agents.

Staphylococcus aureus has been studied extensively in experiments of this kind, and has for the most part shown an increased sensitivity to antibacterial agents with increasing temperature. I have already alluded to the findings of Asheshov of the progressive loss of penicillinase activity of many strains of *S. aureus* after subculturing at 43-44C (62). May, Houghton and Perret (69) have reported similar

findings with a clinical isolate from Western Australia (Figure 12).

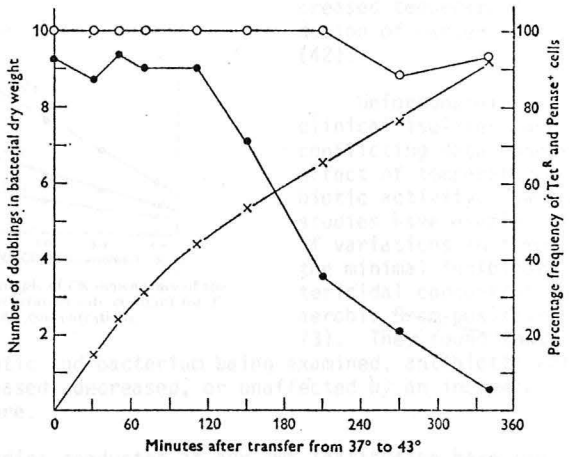


Figure 12. Cumulative growth curve (x—x) and frequency of Tet^R cocci (●—●) and of Penase$^+$ cocci (o—o) of *Staphylococcus aureus* E169 in medium NB-1 following transfer from 37 to 43C (Ref. 69).

Sabath and Wallace (70) have reported that between 0 and 15% more colony forming units of resistant *S. aureus* can be obtained from suspensions subjected to inhibitory levels of methicillin when subcultures are incubated at 25C than at 37C. Thus, the resistance mechanism of *S. aureus* to methicillin, like that to penicillin, appears to be somewhat less active at higher temperatures.

Studies already cited by Muschel, et al (48) have shown that growth of various Gram-negative bacilli at temperatures >37C leads to a progressive increase in susceptibility to cell membrane-active antibiotics and detergents. This increased susceptibility is accompanied in some cases by antigenic changes in the cell wall of the bacteria, which could be responsible for the enhanced antibiotic susceptibility. The kinetics of action of ribosomally active antibiotics on Gram-negative bacilli are also temperature dependent, exhibiting a direct relationship between temperature and antibiotic concentration on inhibition of growth (Figure 13) (71). This phenomenon could reflect either an increased rate of uptake of the antibiotic at higher temperatures or an absolute increase in activity

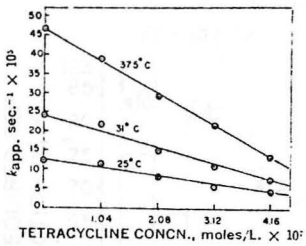


Fig. 13.—Typical example of the dependence of the apparent first-order generation rate constant for *E. coli* growth on antibiotic concentrations.

due to the known effect of increased temperature on degradation of bacterial ribosomes (42).

Unfortunately, studies of clinical isolates have provided conflicting data concerning the effect of temperature on antibiotic activity. Two recent studies have examined the effect of variations in temperature on the minimal inhibitory and bactericidal concentrations of aerobic Gram-positive cocci (72, 73). They found that, depending on the antibiotic and bacterium being examined, antibiotic activity might be increased, decreased, or unaffected by an increase in incubation temperature.

Recent studies conducted at our own institution have provided more quantitative information than previous studies of the effect of temperature on antibiotic activity (46). In these studies, the rates of destruction of various bacteria isolated from clinical specimens at the Dallas VA Medical Center were examined at different temperatures and at different concentrations of antibiotics. Neither the minimal inhibitory concentrations nor the minimal bactericidal concentrations varied by more than one dilution over the temperature range studied in these experiments (i.e., 33-43C). Furthermore, at relatively high concentrations of antibiotic, there was no difference in the rate of destruction of bacteria at different temperatures. However, when relatively low concentrations of antibiotics were examined (i.e., ≃ 1 x the minimal inhibitory concentration), there was an obvious change in the rate of destruction of the test bacteria with change in temperature (Figure 14). This effect could not be accounted for by temperature-related changes in the growth rates of these bacteria. In general, a positive correlation existed between temperature and rate of antibiotic-killing. However, in two cases (ampicillin vs. *E. coli*, and gentamicin vs. *Ps. aeruginosa*), killing rates began to decrease when incubation temperature exceeded 39C. Interestingly, repeated subculturing of *E. coli* at 41C led to a decreased rate of killing of this bacterium by both gentamicin (Figure 14) and ampicillin (Figure 15) at all temperatures tested.

Bacteriocins, like antibiotics, may have enhanced activity at elevated temperatures. Franker, Herbert and Ueda (74) have reported that the bacteriocin of *Actinomyces odontolyticus* (a normal inhabitant of the human oropharynx) is more active at 42C than 37C. Temperature-dependent sensitivity to bacteriocin has been demonstrated in both Gram-

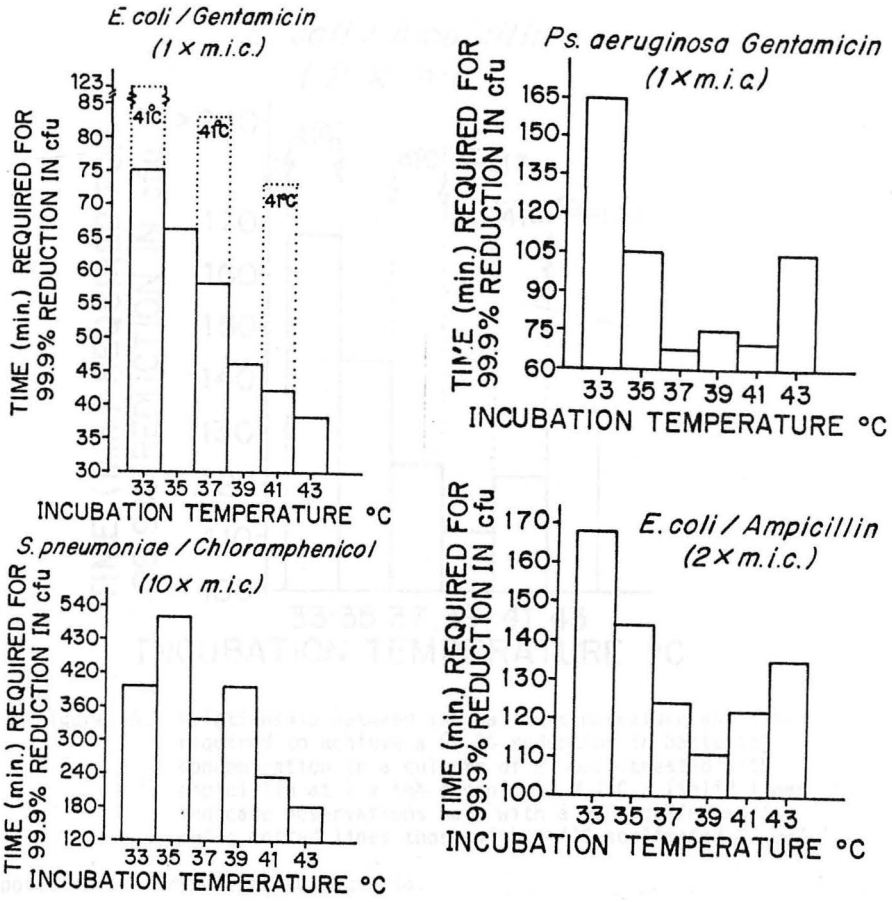


Figure 14. The relationship between incubation temperature and the time required to achieve a 99.9% reduction in bacterial concentration in 4 bacteria/antibiotic combinations. Dotted lines in top left graph indicate observations made with *E. coli* after repeated subcultures at 41C.

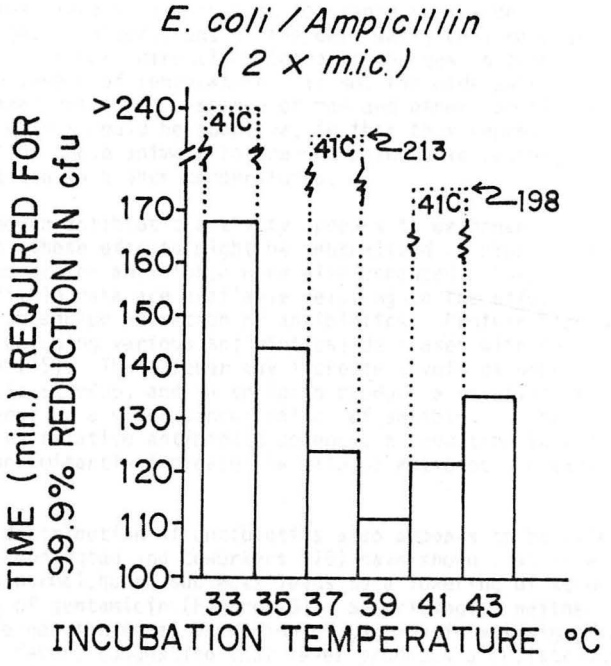


Figure 15. Relationship between incubation temperature and time required to achieve a 99.9% reduction in bacterial concentration in a culture of *E. coli* treated with ampicillin at 2 x the organism's M.I.C. (Solid lines indicate observations made with a 35C acclimated *E. coli*; dotted lines those with a 41C acclimated *E. coli*).

positive and Gram-negative bacteria.

These results and those previously described illustrate both the complexity and the subtlety of the relationship between temperature and the ability of bacteria to resist toxic environments. For the most part there appears to be a positive correlation between temperature and susceptibility of bacteria to antibacterial agents and the various host defenses. However, absolute temperatures may be less important in their effect on antibiotic activity than the magnitude of the change in temperature (i.e., change from the temperature at which the microorganism had been maintained prior to exposure to the antibiotic). By the same token, those changes occurring in the bac-

terium that lead to a decreased tolerance to a wide variety of toxic factors (e.g., alterations of the cell wall, cell membrane, ribosomes, etc.), may be more directly related to changes in temperature than to absolute levels of temperature. If so, the wide swings in temperature that characterize the response of man and other mammals to most bacterial infections could be adaptive, in that they represent an effort on the part of these animals to prevent pathogenic bacteria from becoming acclimatized to higher temperatures.

Although antibiotic activity appears to be enhanced by hyperthermia *in vitro*, these effects might be neutralized *in vivo* if metabolism or excretion of the antibiotic were also enhanced. Surprisingly, relatively little data are available relating to the effect of fever on the metabolism and/or excretion of antibiotics. Protein binding of many drugs (including various antibiotics) decreases with increasing temperature (75). Thus, fever may increase levels of unbound (active) antibiotic *in vivo*, and in so doing produce a relative increase in the potency of a given concentration of antibiotic. However, while increasing relative antibiotic potency, a reduction in protein binding might concomitantly increase the rate of antibiotic clearance by the kidneys.

The distribution of antibiotics also appears to be affected by fever. Pennington and coworkers (76) have shown that fever in both dogs and normal human subjects leads to a lowering of serum concentrations of gentamicin (Figure 16). Surprisingly, neither the serum half-life nor the renal excretion of gentamicin was significantly altered by fever, suggesting that fever produces a redistribution of the drug out of the vascular compartment, and in so doing might induce higher effective tissue levels of gentamicin.

Ladefoged has studied the pharmacokinetics of trimethoprim in normal and febrile rabbits and obtained similar results (77). The serum half-life of trimethoprim did not differ between normal and febrile rabbits, but the volume of distribution of trimethoprim was clearly increased in febrile rabbits. At the present time the clinical significance of these observations is not known. Unfortunately, the effect of fever on the pharmcokinetics of antibiotics in man is largely unexplored.

Viruses: Compared to what is known of the effect on bacteria of variations in temperature within the physiologic range, little is known of its effect on viruses. Some of the earliest attempts to examine the effects of hyperthermia on viruses involved experiments with the polio virus (78). Through these, Lwoff noted that propagation of polio virus in tissue culture resulted in a yield of virus at 37C that was 250 times greater than that at 40C. He also demonstrated that this difference was

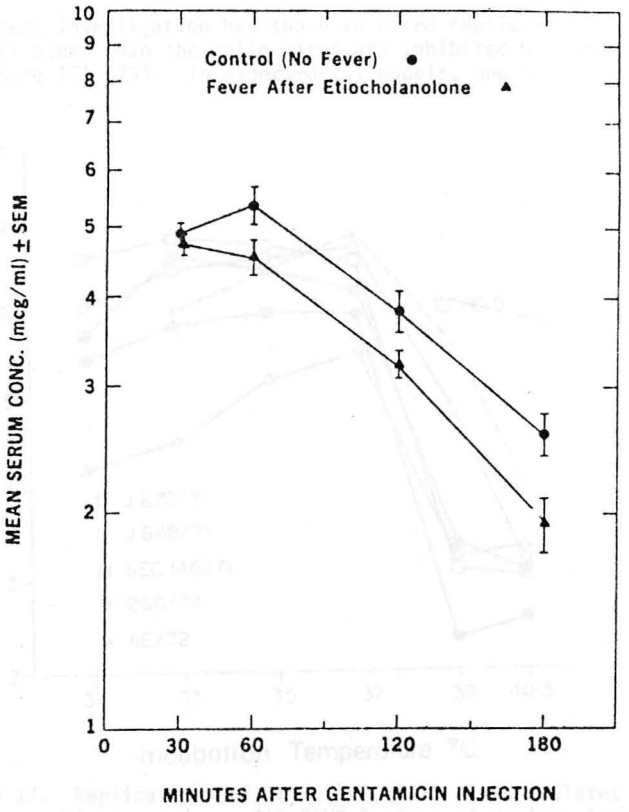


Figure 16. Mean concentrations of gentamicin in serum (μg/ml) for a group of six volunteers were determined at intervals after im injection of gentamicin (1.5 mg/kg). Control levels obtained when the subjects were afebrile are contrasted with those measured when the subjects were febrile after etiocholanolone. (Ref. 76).

not due to an effect of temperature on the culture cells, but upon the virus itself. Unfortunately, it was not clear from his studies by what mechanism inhibition of growth occurred at 40C. However, it did not appear to be the result of simple inactivation of the viral particle. Perhaps most intriguing were his findings that repeated passage of the virus in tissue culture at 41C resulted in an extremely virulent, heat-resistant variant.

More recent investigation has shown *in vitro* replication of many enteroviruses other than the polio virus are inhibited by temperatures of >37C (Figure 17) (79). In experimental models, one such enterovirus,

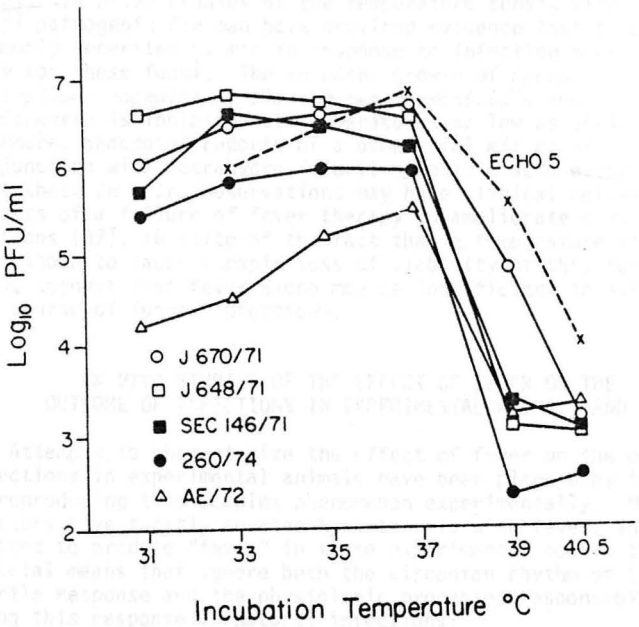


Figure 17. Replicative ability of five E70 virus isolates in comparison with ECHO 5 virus at various temperatures in human WISH cells. (Ref. 79).

Coxsackie B1, is strikingly influenced by temperature (80). Mice which have been made slightly hypothermic by exposure to an ambient temperature of 4C, uniformly succumb to infections with Coxsackie B1. However, mice maintained at 36C (producing a rise in temperature of 2 to 3C) experience no illness and the virus cannot be recovered from these animals.

Elevated temperatures have also been shown to increase resistance of laboratory animals to herpes simplex virus (81), rabies virus (82), transmissable gastroenteritis virus (83), and canine herpes virus (84). These kinds of data have led to speculation that fever may be a major defense mechanism contributing to the recovery of higher animals from primary virus infections (82). It has been suggested that fever might increase

resistance to viral infections by either potentiating other host defenses or decreasing virus replication directly (85). Unfortunately, the crucial question of whether these experimental observations are relevant to clinical disease remains unanswered.

Fungi: *In vitro* studies of the temperature sensitivity of various fungi pathogenic for man have provided evidence that temperatures commonly generated by man in response to infection might be inhibitory for these fungi. The *in vitro* growth of *Sporotrichium shenckii*, *Histoplasma capsulatum*, *Blastomyces dermititidis* and *Paracoccidioides baziliensis* is inhibited at temperatures as low as 38-41C (86). Furthermore, anecdotal reports of a beneficial effect of local heat in conjunction with tetrahydro-fufuryl nicotinic acid ester (86) suggest that these *in vitro* observations may have clinical relevance. However, reports of a failure of fever therapy to ameliorate cryptococcal infections (87), in spite of the fact that a temperature of 39.4C has been shown to cause a rapid loss of viability of this fungus *in vitro* (88), suggest that fever alone may be insufficient to alter the clinical course of fungal infections.

IN VIVO STUDIES OF THE EFFECT OF FEVER ON THE OUTCOME OF INFECTIONS IN EXPERIMENTAL ANIMALS AND MAN

Attempts to characterize the effect of fever on the outcome of infections in experimental animals have been plagued by the problem of reproducing this complex phenomenon experimentally. Many investigators have tacitly equated hyperthermia with fever, and have been content to produce "fever" in these experimental models through artificial means that ignore both the circadian rhythm of the normal febrile response and the physiologic processes responsible for generating this response in natural infections.

Of all the experiments attempting to provide insights into the teliological significance of fever, those of Bernheim, Kluger, and associates involving *Aeromonas hydrophila* infections in the reptile *Dipsosaurus dorsalis*, have been most successful in approximating the natural febrile response of the experimental animal being studied (5,89-92). These investigators first established that *D. dorsalis* responded to challenge with *A. hydrophila* by increasing their thermal set point in a way that was remarkably similar to the febrile response of mammals (5,89). Unlike mammals, however, this poikilotherm is able to raise its body temperature in response to infection only if placed in an environment having an appropriate thermal gradient (Figure 18). By manipulating this gradient, researchers can readily control the body temperatures of the experimental animals. Using this model, Kluger, et al demonstrated a direct corre-

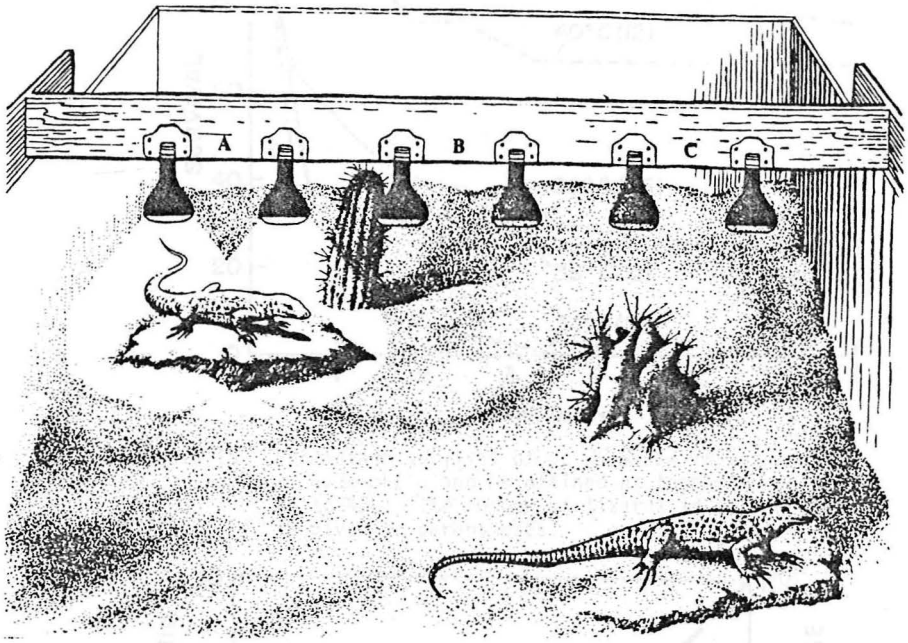


Figure 18. In a study of how lizards respond to infection, an infected iguana in a desert environment sought refuge under heat lamps that warmed the area to raise the body temperature to feverish levels.

lation between body temperature and survival following injection of *A. hydrophila* into the dorsal lymphatic space of *D. dorsalis* (Figure 19) (90). *In vitro* doubling time of *A. hydrophila* was constant between 34 and 40C in spite of the progressive increase in survival (Figure 20). These findings suggested to the investigators that the effect of moderate hyperthermia in reducing mortality was due to an enhancement in host defenses rather than an inhibition of the bacterium. This interpretation was supported by later investigations, demonstrating stimulation by fever of aspects of the early inflammatory response of *D. dorsalis*, leading to increased leukocyte emigration locally and containment of infection (92). Furthermore, whereas fever had a beneficial effect on survival in *D. dorsalis*, suppression of fever by injection of a non-toxic dose of

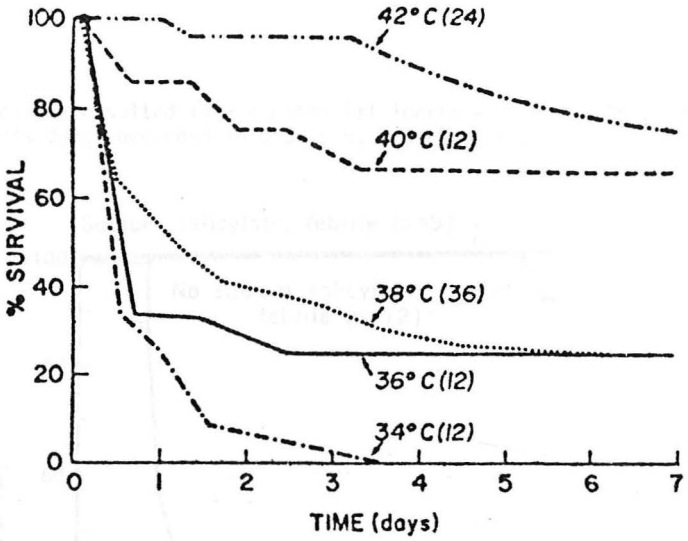


Figure 19. Percentage survival of *D. dorsalis* injected with *A. hydrophila* and maintained at temperatures of 34 to 42C. The number of lizards in each group is given in parentheses.

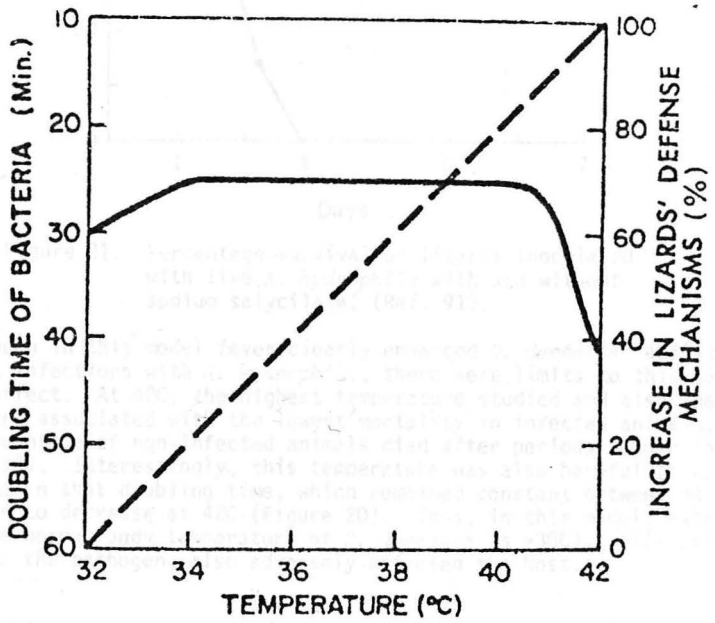


Figure 20. *In vitro* doubling time of *A. hydrophila* (solid line) and theoretical increase in the lizards' defense mechanisms (dashed line) plotted against temperature.

sodium salycilate resulted in a substantial increase in mortality, and only when this drug succeeded in producing antipyresis (Figure 21) (91).

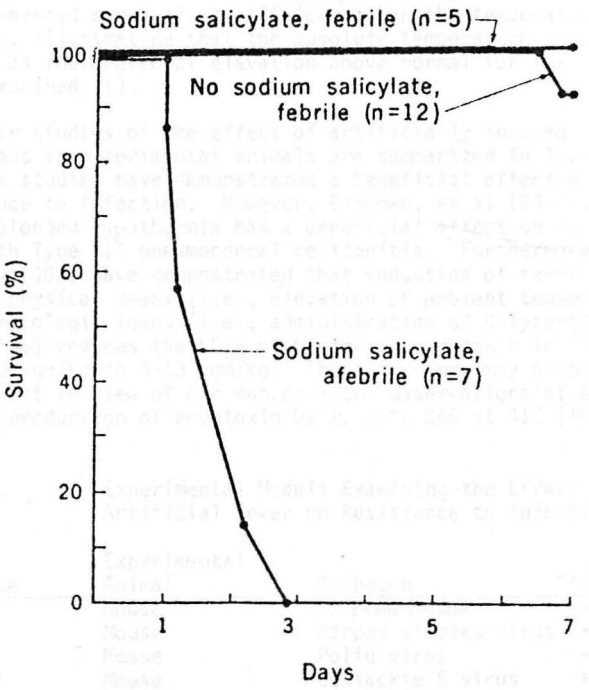


Figure 21. Percentage survival of lizards inoculated with live *A. hydrophila* with and without sodium salycilate. (Ref. 91).

Although in this model fever clearly enhanced *D. dorsalis'* ability to resist infections with *A. hydrophila*, there were limits to this beneficial effect. At 42C, the highest temperature studied and also the temperature associated with the lowest mortality in infected animals, a small percentage of non-infected animals died after periods longer than 3½ days (90). Interestingly, this temperature was also harmful to *A. hydrophila* in that doubling time, which remained constant between 34 and 40C, began to decrease at 42C (Figure 20). Thus, in this model, extreme fever (the normal body temperature of *D. dorsalis* is ≈38C), while deleterious to the pathogen, also adversely affected the host.

Many other studies in both poikilotherms and homeotherms have demonstrated a beneficial effect of artificially induced fever on either resistance to or recovery from infection. Findings similar to those described above have been observed in goldfish given intraperitoneal infections of *A. hydrophila* (93). In this model, fever enhanced survival at ≈10C lower than the temperatures of *D. dorsalis*, illustrating that the absolute temperature is not as important as the degree of elevation above normal for the species being examined (1).

Other studies of the effect of artificially induced fever on infections in experimental animals are summarized in Table 3. Most of these studies have demonstrated a beneficial effect of fever on resistance to infection. However, Eiseman, et al (94) have shown that prolonged *hypo*thermia has a beneficial effect on survival of mice with Type III pneumococcal peritonitis. Furthermore, Atwood and Kass (104) have demonstrated that induction of fever in rabbits by both physical means (i.e., elevation of ambient temperature) and by pharmacologic means (i.e., administration of D-lysergic acid diethylamide) reduces the LD_{50} of bacterial endotoxin in these animals from 240 µgm/kg to 4-13 µgm/kg. These findings may be particularly significant in view of our own *in vitro* observations of an increased rate of production of endotoxin by *E. coli* 055 at 41C (49).

TABLE 3. Experimental Models Examining the Effect of Artificial Fever on Resistance to Infection

Reference	Experimental Animal	Pathogen	Effect*
94	Mouse	*S. pneumoniae*	-
81	Mouse	Herpes simplex virus	+
95	Mouse	Polio virus	+
96	Mouse	Coxsackie B virus	+
82	Mouse	Rabies virus	+
97	Mouse	*C. neoformans*	+
98	Rabbit	*S. pneumoniae*	+
99	Rabbit	*C. neoformans*	+
84	Puppy	Herpes virus	+
83	Piglet	Gastroenteritis virus	+
100	Chicken	*B. anthracis*	+
101, 102	Fish	Hematopoietic necrosis virus	+
103	Ferret	Influenza virus	+

* -: fever associated with decreased resistance; +: fever associated with enhanced resistance.

Surprisingly, almost no reliable data exist regarding the effect of fever on the outcome of infections in man. In a review of 860 patients with bacteremia treated at the University of Minnesota Medical Center between 1958 and 1966, DuPont and Spink found no correlation between temperature and survival (105). Unfortunately, they did not subject their data to statistical testing. In a retrospective analysis of 218 patients with Gram-negative bacteremia, Bryant, et al observed a clear trend toward improved survival with fever (106). Similar findings have been reported by Weinstein, et al in patients with spontaneous bacterial peritonitis (107). Unfortunately, both Bryant and Weinstein analyzed their data using statistical methods poorly suited to the task of testing multivariant clinical observations.

We have recently reviewed the case records of 184 patients with polymicrobial sepsis seen at three Dallas hospitals between 1972 and 1977 (108). The relationships of potential risk factors to outcome were evaluated using log linear models (109), a multivariant method of statistical testing that enables one to measure the individual importance of a given risk factor in (clinical) situations in which many factors may be exerting their effects on outcome simultaneously. Of the risk factors having a significant effect on outcome (i.e., $p<0.05$ by log linear models available), underlying diseases were the most important. However, there was also a prominent (and independent) association between temperature response to the polymicrobial sepsis and outcome, with lowest death rates occurring in patients who manifested a febrile response at the time of onset of sepsis (Table 4). Although

TABLE 4. The Relationship of Temperature Response of Patients with Polymicrobial Sepsis to Outcome

Temperature	Disease Group*		
(°C)	Non-Fatal†	Ultimately Fatal	Rapidly Fatal
<36.1	20(69)	12(92)	6(83)
36.1-<37.2	12(75)	3(67)	2(100)
37.2-<38.3	36(22)	17(65)	4(100)
38.3-<39.4	30(27)	10(60)	7(86)
≥39.4	17(41)	4(50)	4(75)

*No. (% Mortality)
†Association of temperature with outcome significant in this disease group at $p<0.05$ by log linear models analysis.

the correlation between fever and enhanced survival reached statistical significance by log linear models analysis only in the *non-fatal* group, there was also an apparent trend in the *ultimately fatal* group toward

enhanced survival among patients who developed febrile responses. In the *non-fatal* group, the favorable effect of fever on outcome was most pronounced between 37.2 and 39.4C, and appeared to diminish as the peak temperature increased above 39.4C.

The apparent reversal of the beneficial effect of fever on outcome at very high temperatures in patients iwth polymicrobial sepsis is consistent with observations in *D. dorsalis*, that extreme pyrexia may be detrimental to the host as well as to the pathogenic microorganism (90). Observations by Bennett and Nicasti (100) of an increased incidence of extreme pyrexia in patients dying of pneumococcal pneumonia (Table 5) also support the conclusion that moderate fever, but not extreme fever, enhances resistance of higher animals to infection.

TABLE 5. Incidence of High Fevers in 51 Patients with Untreated Type III Pneumococcal Pneumonia.

Patients	Incidence at Rectal Temperature of: 104 F	105 F	106 F	107 F
	%	%	%	%
Recovered (23 cases).....	65	30	17	0
Died (28 cases).....	75	57	39	11

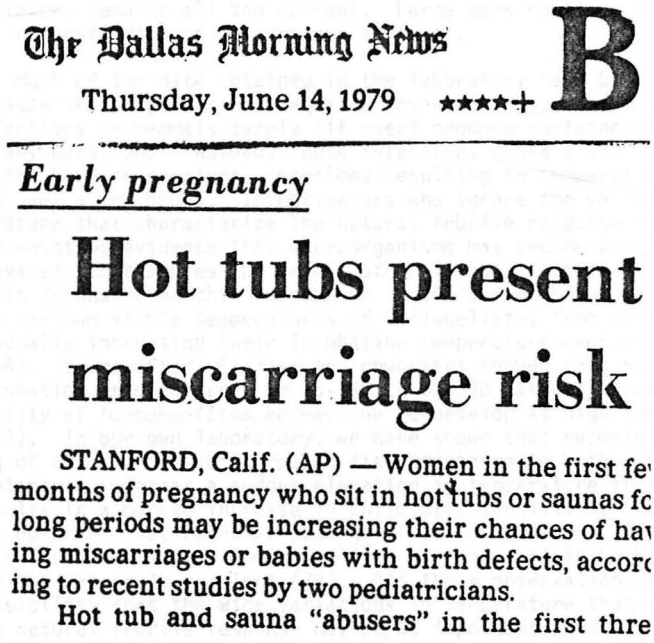
In general, documented adverse effects of high fever on man are few. A variety of metabolic alterations have been observed during the course of fever in man (100). However, the significance of these metabolic changes relative to recovery from infections is for the most part unknown.

Fever has long been recognized as a factor involved in the precipitation of recurrent herpes simplex infections (110). In spite of the apparent capacity for fever to produce relatively inconsequential exacerbations of latent infection in man, resistance to primary herpes simplex infections is increased by fever in experimental animals (81). The effect of fever on resistance to primary herpes infections in man is not known.

Perhaps the most common and potentially devastating complication of fever in man is the febrile convulsion. Approximately 3% of children experience febrile convulsions at one time or another, and as many as 11% developing febrile illnesses between the ages of 6 months and 5 years will experience convulsions (111). Furthermore, these convulsions may result in permanent brain damage.

In 1978, Miller, Smith, and Shepard reviewed the maternal histories of 63 anencephalic infants and obtained histories of maternal hyperthermia

during the 22nd-28th days of gestation (as a consequence of either febrile illness or sauna bathing) in 11% of cases as opposed to 0-0.1% in controls (11). As illustrated in Figure 22, these observations have not gone unnoticed by the lay press. Their contention



The Dallas Morning News B

Thursday, June 14, 1979 ★★★★+

Early pregnancy

Hot tubs present miscarriage risk

STANFORD, Calif. (AP) — Women in the first fe
months of pregnancy who sit in hot tubs or saunas fc
long periods may be increasing their chances of ha
ing miscarriages or babies with birth defects, accor
ing to recent studies by two pediatricians.

Hot tub and sauna "abusers" in the first thre

Figure 22.

that maternal hyperthermia near the presumed time of anterior neural groove closure is supported by numerous studies in experimental models demonstrating an adverse effect of hyperthemia on neural tube development (112-114). Nevertheless, efforts to extrapolate data obtained from studies of experimental animals to man are fraught with danger due to the fact that teratogens are frequently species-specific and often quite exquisitely so (115). The apparent association between sauna bathing and anencephaly is not supported by the reports that Finland, the home of the sauna, has the lowest reported rate of anencephaly of any country in the world.

CONCLUSION

In 1960 Bennett and Nicastri wrote that in spite of its immense clinical importance, fever was "a subject considered less and less in the laboratory of the investigator and more and more in the realm of the turner of neat phrases and composer of aphorisms" (100). Unfortunately, their judgment of the "state of the art" as it pertains to fever, remains all too current. Large gaps continue to exist in our understanding of the process of fever.

Much of the data obtained in the laboratory have been imperfect because investigators have equated fever with hyperthermia. In fact, infections in mammals rarely (if ever) produce sustained hyperthermia of any duration. Instead, these infections cause a waxing and waning of the body temperature, sometimes resulting in temperature shifts of >4C over a few hours. Investigators who ignore the variations in temperature that characterize the natural febrile response also overlook the mounting evidence that microorganisms may become acclimatized to elevated temperatures that might otherwise be inhibitory. Dallinger first demonstrated this phenomenon in 1887, when he was able to raise the maximum viable temperatures of 3 flagellates from 23 to 70C by gradually increasing their incubation temperature over a 7-year period (116). Years later, Frazier and coworkers showed that elevating the incubation temperature from 35-37C to 38-39C markedly increased the ability of *Lactobacillus helvetious* to develop at high temperatures (117). In our own laboratory, we have shown that repeated subculturing of *E. coli* at 41C increases its resistance to both ampicillin and gentamicin, whereas a sudden elevation in temperature from 35C to 41C results in a marked increase in antibiotic sensitivity (46). Lwoff has observed that repeated passage of polio virus in tissue culture at 41C results in the emergence of a variant that is both heat-resistant and extremely virulent (78). All these observations raise the possibility that the wide variations in temperature that characterize the natural febrile response may be as important as the height of the fever in inhibiting pathogenic microorganisms, since they may be necessary to prevent the emergence of heat-resistant variants.

Fever cannot be equated with hyperthermia for the reasons just enumerated, but also because it is a complex physiological process involving much more than a simple elevation of body temperature. Endogenous pyrogen, whose function is to elevate the thermal set point during assaults by various pathogenic microorganisms, also markedly alters iron binding by the host and in this way may rob pathogenic microbes of an essential nutrient (4). Microorganisms are more susceptible to thermal injury in the presence of high levels of oxygen and in an acid environment (41). Thus other features of the inflammatory response (e.g., hyperemia, metabolic acidosis) may act in concert with the hyperthermia of fever to inhibit invading microorganisms.

Because of the complexity of the physiological processes involved in the febrile response, it has been difficult to extrapolate from experimental data to the clinical situation. Nevertheless, the weight of available experimental and clinical data indicates a favorable effect of moderate fever on almost all of the infections that have been studied. Extreme fever (i.e., ≥41C) appears to be detrimental to both the host and the pathogenic microorganism and may be particularly dangerous in neonatal animals because of its effect on the developing brain. Perhaps equally important has been the observation that antipyretic therapy in experimental models has an opposite effect from moderate fever on the outcome of infections, in that antipyresis has been shown to increase mortality in *A. hydrophila* infections in *D. dorsalis* (91), as well as that of pneumococcal peritonitis in mice (118). Clearly, clinical investigations are sorely needed to test the validity of the application of principles established in experimental models to human infections. However, until these provide evidence of an adverse, or even an inconsequential effect of moderate fever on the course of human infections, I would think it wise to reserve antipyretic therapy in infections for pregnant women, neonatal children, and patients exhibiting temperatures in excess of 41C.

# # #

COVER (Ref. 119)

Left: The final writing of *ummu* (Akkadian words meaning "fever and inflammation") *c.*500 B.C.

Proceeding to the right: Progressively earlier forms, until the earliest one (right) turns out to be a Sumerian pictogram for *brazier* (all pictograms rotated 90°).

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