Body Temperature Variability (Part 1): A Review of the History of Body Temperature and its Variability Due to Site Selection, Biological Rhythms, Fitness, and Aging

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Abstract

Body temperature is a complex, non-linear data point, subject to many sources of internal and external variation. While these sources of variation significantly complicate interpretation of temperature data, disregarding knowledge in favor of oversimplifying complex issues would represent a significant departure from practicing evidence-based medicine. Part 1 of this review outlines the historical work of Wunderlich on temperature and the origins of the concept that a healthy normal temperature is 98.6° F/37.0° C. Wunderlich s findings and methodology are reviewed and his results are contrasted with findings from modern clinical thermometry. Endogenous sources of temperature variability, including variations caused by site of measurement, circadian, menstrual, and annual biological rhythms, fitness, and aging are discussed. Part 2 will review the effects of exogenous masking-agents – external factors in the environment, diet, or lifestyle that can influence body temperature, as well as temperature findings in disease states. (*Altern Med Rev* 2006;11(4):278-293)

Introduction

Body temperature is a complex, non-linear variable that is subject to many sources of internal and external variation. While these sources of variation significantly complicate interpretation of temperature data, disregarding knowledge in favor of oversimplifying complex issues would represent a significant departure from practicing evidence-based medicine.

In order for a biomarker of physiology to be properly understood in a clinical or research setting, there must be an accurate understanding of: (1) the expected value or range of values in the healthiest subset of the population; (2) the values or range of values in the sickest or least healthy subsets of the population; (3) how the biomarker changes as a person moves along a continuum of health and disease; (4) known sources of variation that could cause the biomarker to be misinterpreted; and (5) whether the relationship the biomarker might have to a specific condition represents an actual divergence from appropriate function (pathology or disease) or an intentional adaptation to other factors in the diet, lifestyle, or environment (intentional effect).

A significant body of literature on temperature exists that partially helps characterize some of the aforementioned considerations. Unfortunately, much of this research appears to be underappreciated in clinical settings. This review summarizes available temperature research with a goal of clarifying some of the above points. A great deal of the available research on body temperature relates to predictable rhythms, with circadian rhythm studies dominating the research. The discipline that looks at physiology in this manner is often referred to as chronobiology – "scientific discipline concerned with the definition, mechanisms, and significance of the so-called time structure of life forms."[1] Chronobiology presumes

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that "human bioprocesses and functions exhibit predictable variability in time, biological rhythms, at every level of organization."[1]

Body temperature has demonstrated predictable time-sensitive variability. Specific concepts and terminology from this discipline will be introduced to describe the findings.

The Origins of 98.6° F

A widely accepted medical concept is that a normal body temperature for a healthy adult is approximately 98.6° F/37.0° C. The origin of this concept is generally credited to independently conducted research by two different groups in the 19th century – Becquerel and Breschet, followed 33 years later by Wunderlich. While both groups contributed to the concept of 98.6° F being "normal" temperature, medical historians primarily credit the work of Wunderlich and his book, *Das Verhalten der Eigenwarme in Krankheiten (The Course of Temperature in Disease)*, as the definitive work on the subject, giving 98.6° F/37.0° C its special clinical significance in medicine.[2]

Since the origins of 98.6° F/37.0° C can be traced to Wunderlich, it is important to understand what he did and what he observed. Wunderlich is believed to have supervised approximately 25,000 patients at the University of Leipzig's medical clinic. The temperature data recorded on these patients formed the basis for his book. He wrote that, "...when the organism is in a normal condition, the general temperature of the body maintains itself at the physiologic point 37.0° C=98.6° F."[3]

In addition to the above comments, Wunderlich considered body temperatures within a range of 97.2° F/36.2° C to 99.5° F/37.5° C as normal.[4] Wunderlich observed that body temperature increased with mental exertion, constipation, and urinary retention. He also observed slightly higher temperatures in women than in men and significantly lower (0.9° F/0.5° C) temperatures in older individuals. Of considerable importance are Wunderlich's observations that temperature oscillates in both healthy and unhealthy individuals according to the time of day. He wrote, "The lowest point is reached in the morning hours between two and eight, and the highest in the afternoon between four and nine." His published writings suggest an average change of 0.9° F/0.5° C during this oscillation.[5] While Wunderlich's observations of a 98.6° F/37.0° C average temperature became the basis for a 'normal' temperature, his observations on normal temperature variation appear to have been essentially disregarded in clinical medicine.

In addition to these predictable sources of variation, interpretation of Wunderlich's data requires consideration of several other potentially important factors. To obtain his data, axillary temperatures were monitored exclusively. In Wunderlich's writings there is evidence he had lower standards for precision than exist today. He wrote, "Errors which do not exceed half a degree Centigrade are scarcely worth mention."[2] This is a far lower standard of precision than those used in modern clinical thermometry. He also used a thermometer quite different than those used today – one hypothesized to be less precise and calibrated differently. Since the first internationally accepted standards for temperature scales were not adopted until after his death, the calibration of his instruments is uncertain. The only working model of a thermometer (Mutter Museum Thermometer), which is believed to have been used by Wunderlich, produces readings consistently 2.9-3.2° F/1.6-1.8° C higher than those obtained with digital thermometers, and 3.4° F/1.9° C higher than those obtained with a National Bureau of Standards thermometer. The Mutter Museum Thermometer also produces readings that are 2.6-4.0° F/1.4-2.2° C higher than those obtained with other types of 19th century thermometers. These differences in data are consistent with the hypothesis that the thermometers Wunderlich used were not calibrated identically to those in use today.[2]

The final consideration is that, although Wunderlich collected large amounts of data, medical historians have found no evidence to suggest he used principles of statistical analysis on this raw data or that, with existing technology, he could have analyzed more than a small fraction of the total data set. The process used to analyze the data was not described and the actual raw data has never been published in full to allow for statistical analysis.[2]

While Wunderlich's contributions to clinical thermometry cannot be overstated, oversimplification of his observations to one average number (98.6° F/37.0° C) fails to accurately represent his work

Table 1. Normal Temperature Means and Ranges from a Systematic Review of the Literature (1935-1998)

	Oral	Rectal	Tympanic	Axillary
Normal Body Temperature Mean and Range (males)	98.0° F (96.3-99.9) 36.7° C (35.7-37.7)	98.6° F (98.1-99.5) 37.0° C (36.7-37.5)	97.7° F (95.9-99.5) 36.5° C (35.5-37.5)	
Normal Body Temperature Mean and Range (females)	97.2° F (91.7-100.6) 36.2° C (33.2-38.1)	98.6° F (98.2-98.8°) 37.0° C (36.8-37.1)	37.0° C (36.8-37.1) 97.9° F (96.3-99.5)	
Normal Body Temperature Mean and Range (males and females combined)				97.3° F (95.9-98.6) 36.3° C (35.5-37.0)

Adapted from: Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. *Scand J Caring Sci* 2002;16:122-128.

and can lead to misunderstandings when temperatures are monitored clinically. Attention to modern thermometry using readings from more precisely calibrated thermometers at sites including the axilla, oral, and rectal cavities is essential.

Modern Thermometry

Modern thermometry has obtained data at many sites using precise instruments with established calibrations, calling into question the accuracy of Wunderlich's data. For example, 148 healthy men and women ages 18-40 years, participating in the Shigella Vaccine Trials at the University of Maryland Center for Vaccine Development, had oral temperatures measured 1-4 times daily for three consecutive days using an electronic digital thermometer. The mean observed oral temperature was 98.2° F/36.8° C. The reported findings also indicate mean temperature in the group varied diurnally, with a 6 a.m. nadir, a 4-6 p.m. zenith, and a mean amplitude of variability of 0.9° F/0.5° C. Although oral rather than axillary temperatures were monitored, the researchers observed precisely the same type of time-of-day temperature oscillation and amplitude change in temperature as Wunderlich; however, the mean and range of diurnal temperatures were shifted significantly lower.[4]

Sund-Levander et al conducted the largest systematic review of temperatures using data from studies published between 1935 and 1998. Findings of normal temperature means and ranges for males and females are summarized in Table 1.[4] This comprehensive review of the literature indicates that, similar to Wunderlich's actual observations, normal temperature occurs within a range of values and is dependent on the site monitored. Only seven of 37 data sets meeting inclusion criteria for accuracy and reliability reported av-

erage values of body temperature equal to or above 98.6° F/37.0° C; six of these seven reported rectal-temperature data. They also reported that after summarizing the available data from the different studies "... no mean value exceeded 37.0° C, irrespective of place of measurement." The reported range was wider than that reported by Wunderlich at several sites and consisted of temperatures with a lower spectrum of values. For example, Wunderlich reported 98.6° F was the average value of axillary temperatures and the normal temperatures at this site ranged from 97.2-99.5° F/36.2-37.5° C. After reviewing the literature, Sund-Levander reported a slightly wider range of 95.9-98.6° F/35.5-37.0° C; however, the high point of the range was consistent with the mean value of Wunderlich's data.[6]

Overall, their review suggests each site has its own range, and the normal range found at the axilla is significantly lower than that reported by Wunderlich. It seems reasonable that use of clinical thermometry needs to be based on a better understanding of these site-specific differences.

Sources of Temperature Variation

When Sund-Levander et al conducted the systematic review of temperature data, one finding was, although the site where temperature was measured was routinely noted, the time of day, season, and other currently known sources of temperature variation were rarely indicated. Identifying internal and external sources of temperature variability and characterizing the nature of the changes produced by these sources of variability is a relatively new endeavor. It has been increasingly understood within the scientific community over the past two decades that biological variability is a defining characteristic of living organisms. With this understanding has come a tremendous increase in attempts to understand variability of physiological parameters, including body temperature.

One overlooked aspect of Wunderlich's original findings is that he actually did identify several sources of temperature variability, including the time of day. The time-of-day variation in body temperature was observed prior to his work, having been reported at least twice in the middle of the 19th century.[7,8] More recent research indicates time of day is a predictable source of temperature variation and is believed to represent an internal source of temperature variability driven by a circadian pacemaker. Rather than ignoring the temperature variability that Wunderlich and others observed, researchers now realize that understanding circadian and other sources of internal and external variability is essential if temperature data is to be interpreted accurately. Several of the best characterized sources of variation are summarized in this section.

Definitions

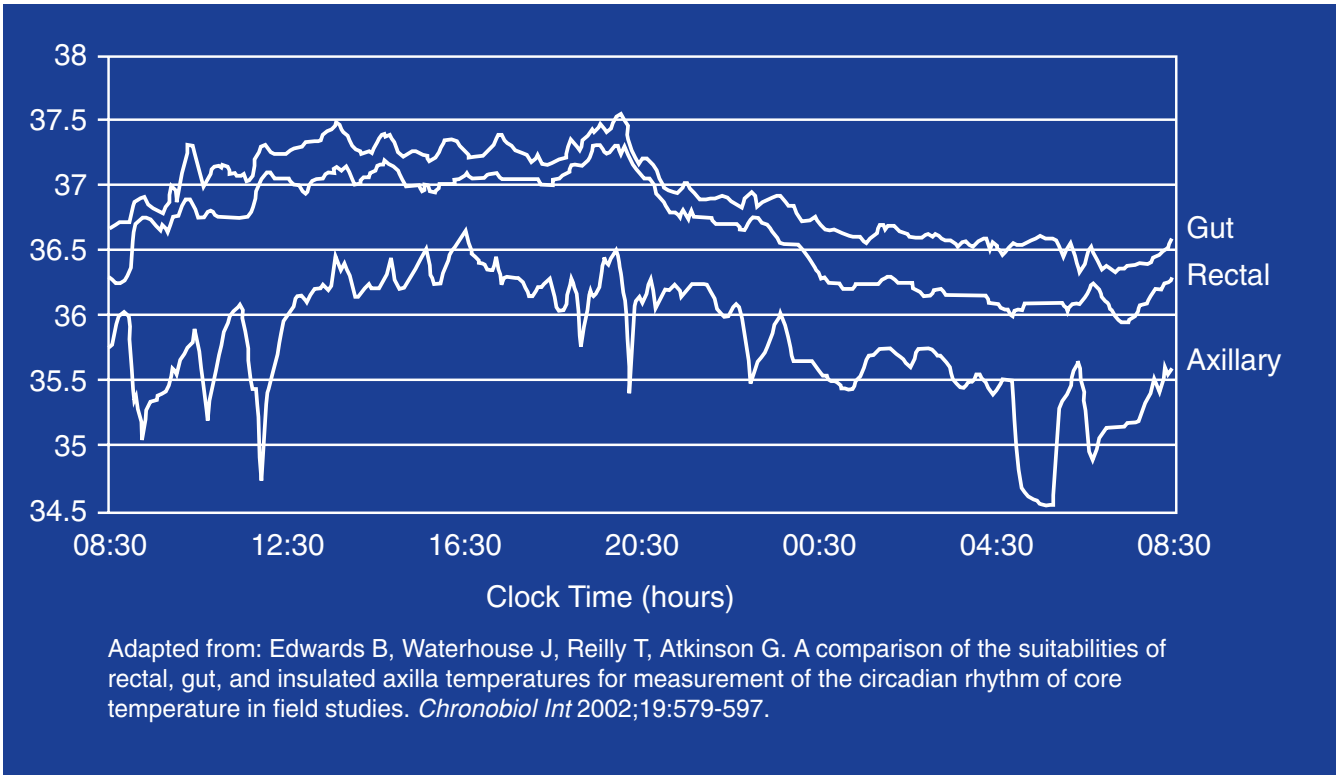
*Note: Acrophase, Amplitude, and MESOR are standardized terms used for describing chronobiological rhythms. These terms are defined as:

ACROPHASE: Measure of the crest time of a rhythm from the cosine curve best fitting the data. It provides the timing of a rhythm in relation to a defined reference point of time. Local midnight is often used for time point for circadian rhythms. It can be expressed in degrees (360°=1 period) or time units (hours and minutes for circadian rhythms, days or months for longer rhythms).

AMPLITUDE: One half of the extent of the change in height of a wave (the difference between the maximum height of the wave and the rhythm-adjusted mean [MESOR] of the wave form).

Midline Estimating Statistic of Rhythm (MESOR): The value midway between the highest and lowest values of the (cosine) function best fitting to the data.

Figure 1. Simultaneous Gut, Rectal, and Axillary Temperatures



Adapted from: Edwards B, Waterhouse J, Reilly T, Atkinson G. A comparison of the suitabilities of rectal, gut, and insulated axilla temperatures for measurement of the circadian rhythm of core temperature in field studies. *Chronobiol Int* 2002;19:579-597.

Variations from Thermometer Placement

Temperature can be monitored at different sites, with the choice of site resulting in certain trade-offs in terms of convenience and reliability. As an example, oral temperature is generally considered to be extremely convenient and reliable, while axillary and other skin surface (tympanic or thoracic) temperatures are convenient but generally considered less accurate. Being an internal measurement, rectal temperature is very reliable and is usually considered the "gold standard" although the least convenient. Gut temperature, obtained via an ingested pill, is also considered to be relatively convenient and to closely approximate rectal temperature.[9]

Studies have attempted to characterize concurrent temperature at various sites. For example, rectal and gut temperatures are considered comparable in terms of mesor, amplitude, and acrophase. Oral temperature closely parallels rectal temperature in terms of amplitude and acrophase; however, the mesor is shifted lower since, at all time points, oral temperature tends to be lower than rectal temperature. Axillary temperature, on the other hand, has a reported lack of parallelism to both oral and rectal temperatures. Not only is mesor lower, but the acrophase in axillary temperature is slightly out of phase with rectal and oral temperatures, and the amplitude is less likely to be characterized accurately because of a greater degree of minute-to-minute variability in axillary temperature. The divergence of axillary temperature from rectal temperature is especially prominent in the morning and evening hours. These points are illustrated in the research reviewed below.

Rabinowitz et al, reporting on rectal, oral, and tympanic membrane temperature measurements from 22 healthy subjects, found mean rectal temperature exceeded concurrent oral readings by 0.72° F/0.4° C and tympanic membrane readings by 1.5° F/0.8° C. The researchers also reported that tympanic membrane readings were significantly more variable (both intrasubject and between subjects) than rectal or oral readings, which had a high degree of parallelism in readings.[10] Hamilos et al reported simultaneously re-

corded rectal temperatures were 0.83° F/0.46° C higher than oral electronic temperatures.[11]

A lack of correlation between oral and axillary temperatures was reported by Agarwal et al. They monitored temperatures of 100 individuals, including 26 who had fever ranging from 99.1-105° F/37.3-40.5° C. As expected, oral temperature was higher than axillary temperature in all cases; however, there was no correlation between the two. The researchers concluded that, "No attempt must be made to extrapolate the axillary to the oral temperature."[12]

Edwards et al recorded temperatures from eight healthy males for 13 days using an ingested pill and a thermally insulated skin probe (minimizing perturbations in data due to ambient air) to record gut and axillary temperatures, respectively. They compared this data to simultaneously collected data of rectal temperatures, recorded at six-minute intervals from the three sites (Figure 1). While rectal and gut temperatures paralleled each other closely, the same degree of parallelism was not observed between rectal and insulated axillary temperatures. As expected, axillary temperature was significantly lower than rectal temperature at all time points, resulting in a significantly lower mesor. And while the overall shape of the temperature pattern was approximately the same, the variability of axillary temperature was substantially greater than for rectal temperature. This variability was most pronounced in the morning and early afternoon hours (until approximately 14:00) and again in the late evening hours (after approximately 19:00) where axillary temperatures changed (up and down) by as much as 1.8-2.7° F/1.0-1.5° C over an hour time interval; while rectal temperatures were holding relatively steady – varying up and down by no more than 0.2-0.5° F/0.1-0.3° C. This was observed in the records of raw data from individuals and from the group's rectal temperatures as a whole. The lack of parallelism between axillary and rectal temperature was particularly marked at the time periods surrounding rising and retiring, making axillary observations most unreliable at these time periods.[13]

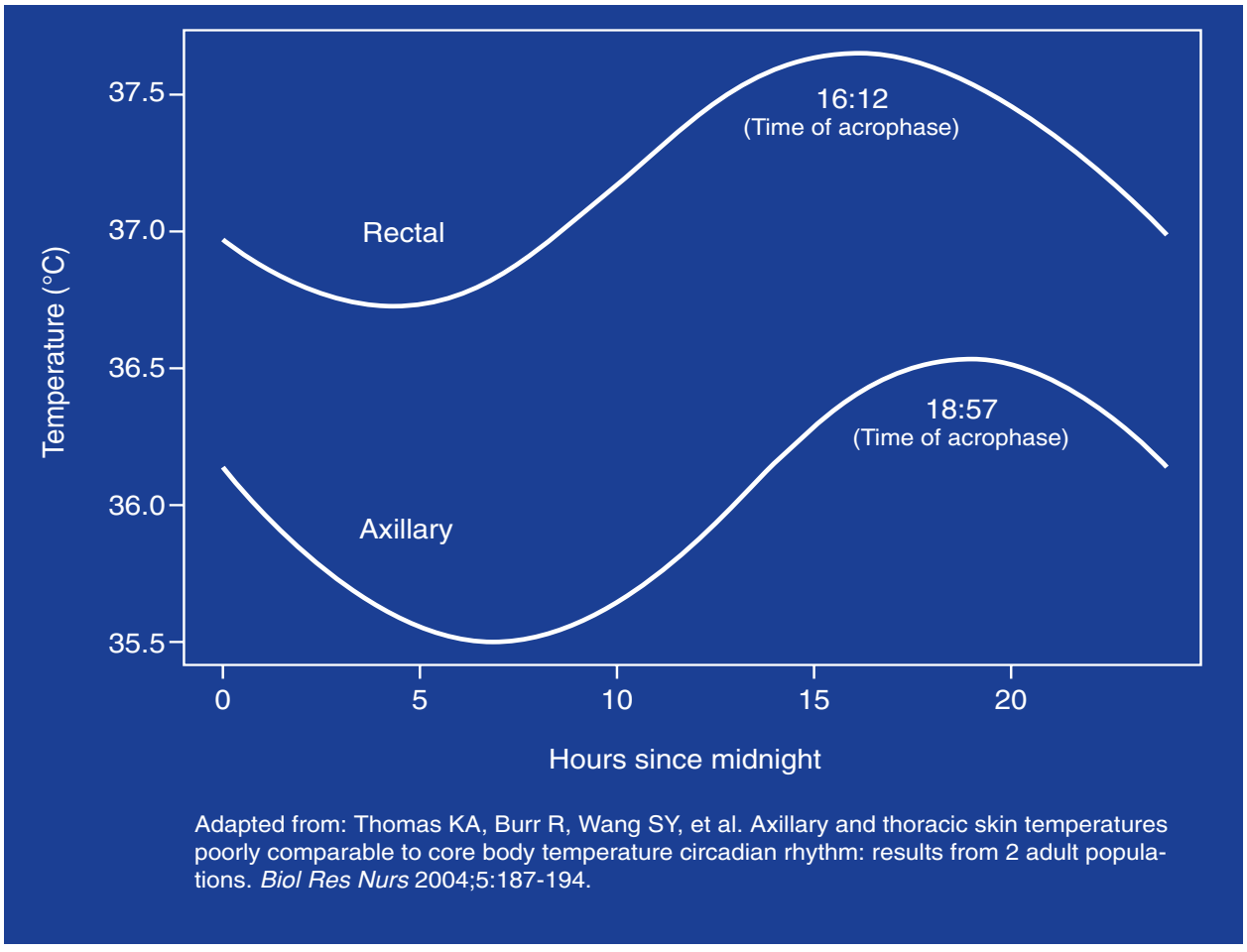
Thomas et al conducted a study comparing simultaneous temperatures collected from the rectum and axilla, recorded continuously for 24 hours while subjects carried out normal activities. The observed circadian parameters of temperature are listed in Table 2. Circadian analysis of the data indicated a comparable amplitude; however, axillary temperatures had a far higher variance and range over comparable periods of time compared with rectal temperatures, making characterization of any individual's amplitude using axillary data far less reliable. As expected, the data obtained was lower at all time points for axillary readings, resulting in a significantly lower mesor. The circadian timing of axillary temperatures did not closely approximate that of rectal temperatures, with the acrophase (high point of the circadian rhythm) for the group shifted several hours later for axillary temperatures. The researchers concluded that their observations do not support the use of axillary temperature as a substitute for rectal temperature.[14] Consistent with these studies, Bogh et al also found that axillary temperature is not a reliable substitute for rectal temperature when determining circadian changes.[15]

Table 2. Comparison of Circadian Characteristics of Simultaneously Recorded Rectal and Axillary Temperatures

	Rectal	Axillary
Mesor	98.94° F (37.19° C)	96.82° F (36.01° C)
Amplitude	0.85° F (0.47° C)	0.92° F (0.51° C)
Acrophase	16:12	18:57

Adapted from: Thomas KA, Burr R, Wand SY, et al. Axillary and thoracic skin temperatures poorly comparable to core body temperature circadian rhythm: results from 2 adult populations. *Biol Res Nurs* 2004;5:187-194.

Figure 2. Cosinor Analysis of Simultaneous Rectal and Axillary Temperatures



Adapted from: Thomas KA, Burr R, Wang SY, et al. Axillary and thoracic skin temperatures poorly comparable to core body temperature circadian rhythm: results from 2 adult populations. *Biol Res Nurs* 2004;5:187-194.

In addition to site-to-site differences, even within the same site there is potential for significant variation, which might be exacerbated by the type of thermometer being used. Erickson reported oral temperatures varied depending on the site and type of thermometer used. When measured with a rapidly responding electronic thermometer, temperatures in the right and left posterior sublingual pockets were 0.3° F/0.16° C higher in afebrile subjects, and approximately 0.4° F/0.23° C higher in those with fever, than when the thermometer was placed in the area under the front of the tongue. With a mercury thermometer, temperature differences were small and not statistically significant. He also reported, when comparing one posterior sublingual pocket to the other, there was no significant difference between temperatures on the left and right side. These findings suggest the importance of using the posterior sublingual pocket as the site for oral temperature measurement and the value of using the same instrument to obtain repeated measurements if attempting to make meaningful comparisons in data.[16]

Singh et al investigated the variation of axillary temperature on left and right sides of the body using an electronic thermometer and compared this data to oral temperatures. Axillary temperatures could be identical on both sides of the body, but also could differ by as much as 3.4° F/1.9° C.[17]

Rectal temperature is an adequate estimate of core body temperature and displays circadian patterns in parallel with other measures of core temperature. The same appears true for gut and oral temperature; however, the mesor is lower for oral temperatures and would need to be factored into any interpretation. Correlations between axillary temperature and rectal temperature are far lower, with a noted lack

of parallelism at many time points, suggesting this site is not comparable for predicting the relationship between observed temperature and actual core body temperature, even if adjustments are made for the lower mesor of the axillary site. Overall, data support using rectal, gut, or oral temperatures. Axillary and tympanic temperatures, on the other hand, do not appear to be suitable substitutes because of the lack of parallelism at these sites and because they don't reflect core body temperature. The significant degree of variability depending on side of the body used to obtain axillary temperature (at least with electronic thermometers) is also a concern, rendering much of the data obtained at this site unreliable.

Variations Due to Circadian Rhythms

Circadian rhythms are biological functions of approximately 24 hours length and are a significant source of body temperature variation. The daily pattern of body temperature is the most widely assessed circadian rhythm in chronobiological studies. It is usually considered a "marker rhythm" and is used to determine time on an individual's body clock and as a reference point to determine whether other rhythms are synchronized or desynchronized.

As mentioned, an under appreciated aspect of Wunderlich's original findings is the observation of consistent time-of-day temperature variation.[5] Time-of-day variation in body temperature had also been observed prior to his work,[7,8] and has consistently been observed in modern investigations. It is estimated that approximately 2,700 publications on circadian rhythms of temperature were published between 1967 and 1990.[18] Several thousand citations on Medline since 1990 also exist for this topic. Because of the robustness of this rhythm and the relative ease of continuous monitoring, body temperature is often used as a "marker rhythm" in circadian research to gain understanding of the overall performance and synchronization of 24-hour biological rhythms.

Daily body temperature, independent of site of measurement, is non-linear and characterized by moment-to-moment complex variability. Figure 1 presents 24-hour data obtained simultaneously from gut, rectal, and axillary sites; the complex variability and the overall circadian pattern of body temperature are evident. Figure 2 shows temperature data obtained simultaneously from rectal and axillary sites after a best fit has been created by cosinor analysis. Cosinor analysis allows the circadian rhythm of body temperature to be described in a simple cosine wave, which is typically characterized in terms of acrophase, amplitude, and mesor. When presented in this format the complex variability of temperature data is filtered out.

Under stable 24-hour, day-night lighting conditions, temperature has a period of 24 hours. However, when exposure to external entraining agents (zeitgebers) is removed, the period of temperature can slightly exceed 24 hours.[19] This is described as a "free running" rhythm since the slightly longer than 24-hour rhythm of temperature is out of phase (desynchronized) from a 24-hour day. Entraining agents include light-dark cycles and meal timing. In individuals entrained to natural light-dark cycle conditions with a wakeup time at 07:00 and bedtime at 23:00, rectal body temperature reaches its lowest value (nadir) about three hours prior to waking and has a high value (acrophase) approximately 12-14 hours after waking. In healthy subjects this cycle repeats daily as long as entrainment is maintained.

As general guidelines the daily temperature nadir is between 03:00-06:00 and the temperature acrophase is usually observed between 16:00-21:00. The difference between the peak and trough of these values would be expected to approximate 1.8° F/1.0° C; however, they can be significantly greater or less than these mean values because of many different factors. The temperature mesor depends on the site monitored, age of the subject, and other factors.[18,20-22]

In order to accurately characterize the endogenous rhythm of body temperature, research settings often use constant routine, forced desynchrony, and mathematical purification methods. While this allows characterization of endogenous rhythmic cycle and temperature changes over the cycle, an individual's body temperature rhythm will be influenced by many endogenous features of the environment as well as health status. As a result, the expected timing of the nadir and acrophase, value of the mesor, and amplitude of this rhythm can be significantly different in an individual under natural conditions.[23] Exogenous masking factors and disease conditions that might influence temperature rhythms will be discussed in detail in part 2 of this article.

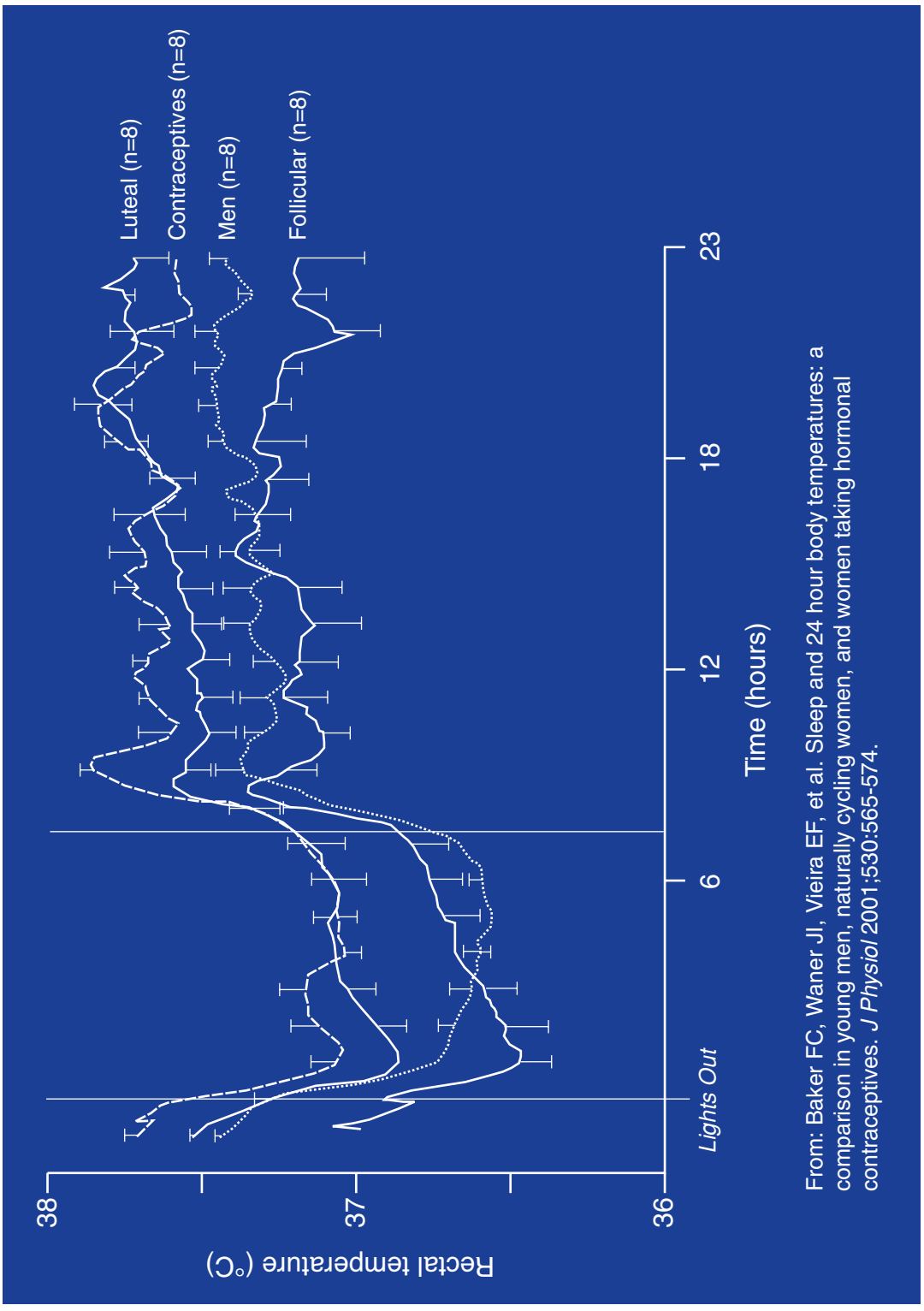


Figure 3. 24-Hour Rectal Temperatures from Naturally Cycling Women in the Follicular and Luteal Phase, from Women Taking Contraceptives, and from Men

From: Baker FC, Waner JI, Vieira EF, et al. Sleep and 24 hour body temperatures: a comparison in young men, naturally cycling women, and women taking hormonal contraceptives. *J Physiol* 2001;530:565-574.

Menstrual Variations

Body temperatures vary in a predictable manner across the menstrual cycle in a normally cycling female. Unlike most other sources of temperature variation, menstrual cycle variation is well known within clinical medicine, is often factored into temperature interpretations, and has been used for fertility planning purposes. The menstrual cycle variation

of a biological rhythm is known as a circamensal rhythm and has a period approximately equal to the length of one menstrual cycle.

Statistically significant circamensal rhythms in body temperature exist. The acrophase (period of overall highest body temperature) occurs during the luteal phase, with a range that can extend from just prior to several days after ovulation. When body temperature is measured immediately after waking and before activity, an increase in temperature ranging from 0.5-1.0° F/0.25-0.5° C is typically observed at or around ovulation. This first-morning rise in temperature is most commonly observed the day after ovulation but can precede ovulation or occur three or more days following it. The menstrual basal body temperature acrophase (timing of the high point in first-morning temperature) can vary from subject-to-subject and even from cycle-to-cycle in the same woman.[24,25]

First-morning body temperature is not the only aspect of temperature that varies with the menstrual cycle. Because the circadian rhythm of body temperature also persists throughout the menstrual cycle, the menstrual cycle acts to layer one rhythm on top of an existing rhythm. Although a circadian rhythm persists, it is notably different in the luteal phase. Not only is body temperature during the luteal phase characterized by a higher waking temperature, it also demonstrates a higher mean daily temperature. A naturally cycling woman maintains a similarly shaped circadian body temperature curve in both the follicular and luteal phases; however, the entire curve is shifted upward by approximately 0.9° F/0.4° C in the luteal phase compared with the follicular phase.[26] Although there is an upward shift in the waking, mean, and overall temperature curve, the difference between peak and trough values can decrease during the luteal phase compared to the follicular phase. The decrease in amplitude occurs because the increase in trough value with ovulation is not accompanied by the same degree of increase in peak temperature values, resulting in a lessening of the difference between the two values.[27]

Timing of the circadian body temperature nadir and acrophase also shifts during the luteal phase. Baker et al reported that, despite going to bed at a similar time, naturally cycling women reached their minimum temperatures 124 minutes after lights out in the follicular phase but only 74 minutes after lights out in the luteal phase. As comparison, the researchers reported women taking hormonal contraceptives reached minimum temperatures 215 minutes after lights out, while men reached minimum temperatures 258 minutes after lights out.[26]

In one of the most detailed investigations on circadian changes in body temperature occurring across the menstrual cycle, Coyne et al had volunteers ingest sensors to accurately monitor core body temperature. After calculating the mesors for circadian temperatures obtained in different parts of the menstrual cycle, it was observed that the circadian mesor for core body temperature is highest in the luteal phase (99.3° F/37.39° C) and lowest in the preovulatory phase (98.4° F/36.91° C). It was 98.7° F/37.08° C during the follicular phase. Similar to other observations, the amplitude of circadian temperature was significantly reduced in the luteal phase compared to all times of the menstrual cycle.[28]

Use of oral contraceptives appears to significantly change daily temperature minimums, maximums, and amplitudes. Figure 3 shows 24-hour rectal temperatures from naturally cycling women in the follicular and luteal phase, from women taking contraceptives, and from men. Oral contraceptives are also believed to abolish the circamensal rhythm of body temperature. Baker et al reported the body temperatures of women taking hormonal contraceptives maintained a similarly shaped circadian body temperature curve to that found in naturally cycling women; however, the entire curve was shifted upward by approximately 1.08° F/0.6° C.[26]

Circamensal rhythm variations in body temperature are attributed to shifts in hormones that occur during the menstrual cycle. Experiments indicate that progesterone has an overall effect of increasing body temperatures, while estrogen has a lowering effect. The portion of temperature variation attributed to menstrual cycle variation has, because of various experimental protocols, been largely determined to result from shifts in the progesterone/estrogen ratio. The circamensal acrophase occurring during the luteal phase is considered to be a result of increases in progesterone levels; temperatures remain elevated as long as progesterone levels are increased.[29-33]

The reliability of using the menstrual cycle rhythm of basal body temperature (morning waking temperature) for fertility planning purposes is a subject of debate. Moghissi et al compared basal body temperature recordings and correlated them with serum luteinizing hormone (LH), progesterone, and estradiol. They reported that basal body temperature failed to accurately predict ovulation in about 20 percent of cycles observed.[34,35] Buxton and Engle reported that in one-third of cases they observed the menstrual cycle rise in basal body temperature occurred more than 24 hours after ovulation had taken place.[36] These and other studies have raised reasonable concerns about the reliability of basal body temperature monitoring for birth control/fertility planning. The reason for this lack of reliability is that other confounding sources of variability exist. This was highlighted by McCarthy and Rockette, who concluded that, "The prediction of ovulation solely with the basal body temperature graph is not useful because of the day-to-day variability of temperature readings, cycle variability and the effects of illness, medication, diet and changes in sleeping patterns."[37]

Seasonal (Annual) Variations

Several studies suggest that the time of year might be a possible source of temperature variability; however, observations from available studies are inconsistent. The lack of agreement might be secondary to the site monitored, the population studied, geography, ambient temperatures, or other confounding factors.

Horne and Coyne monitored oral temperature in 26 subjects in December, March, and June; temperatures were recorded at 30-minute intervals from awakening until bedtime. In males, average daily temperatures were the same in all three months; however, females' average oral temperatures decreased slightly from March (98.4° F/36.9° C) to June (98.2° F/36.8° C) to December (98.1° F/36.72° C). Temperature change from waking to acrophase was reduced in June compared with December, suggesting the temperature amplitude might be diminished in summer compared with the winter season. The acrophase of peak body temperatures occurred slightly later in the day in March (~20:00) and June (~20:00) than in December (~19:00).[38]

Cisse et al recorded rectal temperature data in young healthy male adults in June and December, reporting an increase in the mesor of daily temperatures in June (98.78° F/37.10 °C) compared to December (98.33° F/36.85° C). Daily amplitude of temperature was also greater in June (2.47° F/1.37° C) than December (1.53° F/0.85° C).[39] Kleitman et al observed higher individual and group body temperature levels among young adults in June than in April, noting that subjects with higher temperature levels showed smaller seasonal variations.[40]

Honma et al monitored rectal temperature for five consecutive seasons in 10 healthy male subjects and reported a higher summer 24-hour mean rectal temperature than that recorded in the winter. The data indicated the amplitude of daily temperature was similar in all seasons and the acrophase shifted in the opposite direction of that reported by Horne and Coyne, with the time of temperature acrophase shifted 83 minutes earlier during the summer.[41]

Levendosky et al reported the overall temperature profiles of subjects observed were significantly lower in the summer. However, similar to the observations of Honma et al, daily temperature amplitudes were not different between summer and winter.[42]

Touitou et al explored the seasonal rhythms of rectal temperature in elderly subjects. In elderly men and women the highest temperatures were observed in January and the lowest in June; the circadian mean from January was 98.63° F/37.02° C for elderly men and 98.71° F/37.06° C for women. In June the mean temperature was 98.15° F/36.75° C and 98.08° F/36.71° C for men and women, respectively. The result was a circannual rhythm with a mesor of 98.28° F/36.82° C in men and 98.35° F/36.86° C in women, with a circannual amplitude of 0.41° F/0.23° C and 0.29° F/0.16° C in men and women, respectively. In these elderly subjects the amplitude of daily temperature also shifted throughout the year. Amplitude of circadian temperature data was significantly greater in June (0.52° F/0.29° C in men and 0.60° F/0.34° C in women) than in January (0.36° F/0.20° C in men and 0.22° F/0.12° C in women). Since amplitude represents half the peak-to-trough value, this suggests that in elderly subjects the daily peak-to-trough difference can be noticeably greater in summer than winter.[43]

While each of the above studies noted significant seasonal variability in body temperature

parameters, there was an overall lack of agreement from study to study in terms of the nature of the variability. Additional research is warranted to better categorize the seasonal rhythm of body temperature and to clarify existing contradictions.

Variations Due to Physical Fitness

Increased physical activity appears to significantly influence body temperature. Atkinson et al reported that daily amplitudes of oral temperatures for physically active individuals were higher than those observed in inactive subjects. After categorizing participants as physically active or inactive on the basis of habitual leisure-time physical activity, oral temperatures were measured at 02:00, 06:00, 10:00, 14:00, 18:00, and 22:00. The physically active group had lower oral temperatures at 02:00 and 06:00 and similar or higher oral temperatures at other time points. The minimum oral temperatures occurred at the 06:00 reading and were approximately 95.4° F/35.2° C and 96.08° F/35.6° C for the physically active and inactive groups, respectively. Oral temperature maximums occurred during the evening in both groups and were approximately 97.3° F/36.3° C. As a result, the difference between the minimum and maximum oral temperature was significantly greater in the physically active than the inactive group.[44]

Physical activity also appears to make the circadian time structure of body temperature more resistant to phase shifts. Mauvieux et al reported that athletic subjects were more resistant to circadian phase shifts under shift work conditions, maintaining a stability of period and acrophase to a far greater degree than less athletic subjects.[45]

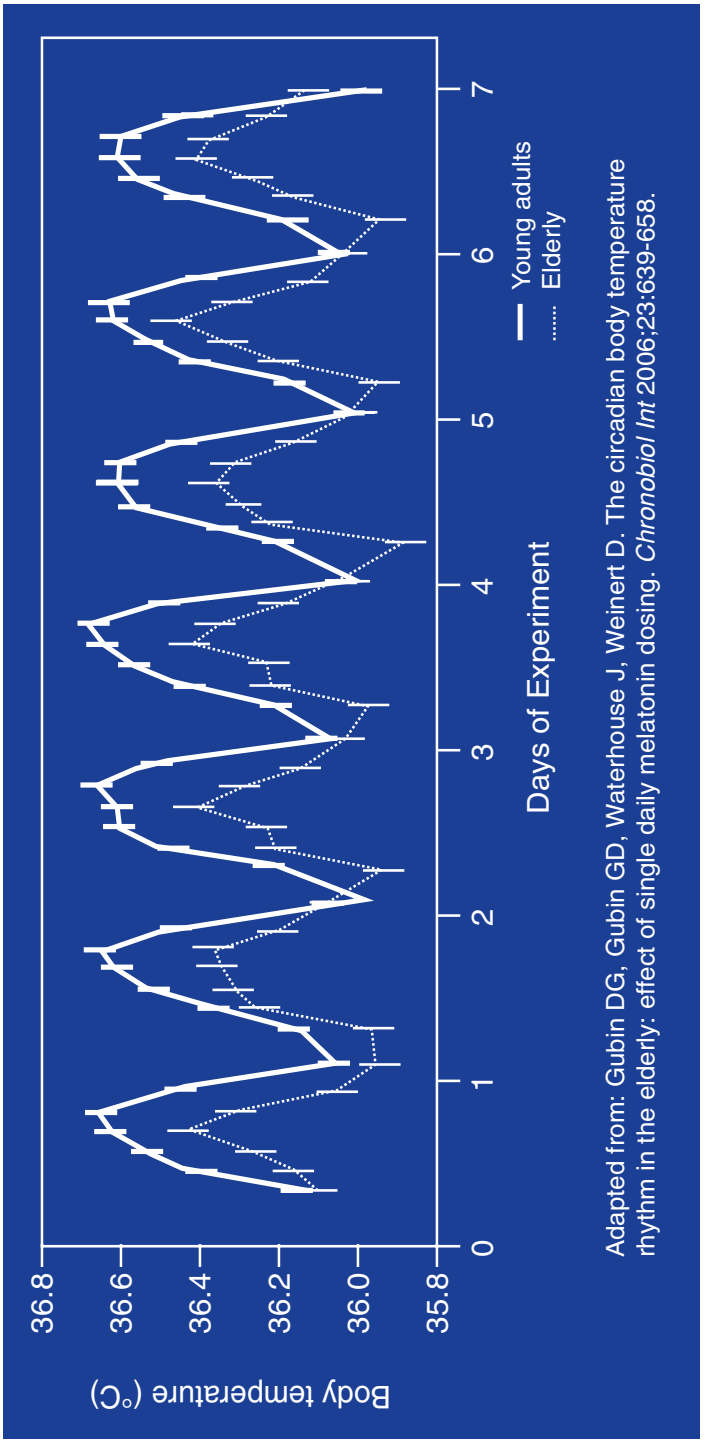


Figure 4. Seven Days of Axillary Temperature Data from Young and Elderly Adults

Adapted from: Gubin DG, Gubin GD, Waterhouse J, Weinert D. The circadian body temperature rhythm in the elderly: effect of single daily melatonin dosing. *Chronobiol Int* 2006;23:639-658.

Variations Due to Aging

Adult body temperature lies within a range of time-dependent possible values; however, this range might be influenced by age. There is some evidence that daily temperature mesor and amplitude decrease with aging.

In a group of 105 females with an age range of 61-105 years, Howell obtained oral temperatures with an electronic thermometer and reported a group mean of 96.8° F/36° C. This is significantly lower than what would be expected in a younger population.[46] Touitou et al, exploring the biological rhythms of rectal temperature in healthy young and elderly subjects, found daily body temperature amplitude was reduced in the elderly subjects.[43]

Mason et al recorded circadian parameters of body temperature in 18 healthy women, ages 65-80 years. Oral temperature readings were monitored using an electronic thermometer every two hours during waking hours for seven consecutive days. Individual temperature daily mesors ranged from 96.6-98.3° F/35.9-36.8° C, amplitudes ranged from 0.22-0.99° F/0.13-0.56° C, and group mean amplitude was 0.53° F/0.3° C, resulting in an average peak-trough difference of 1.03° F/0.58° C.[47]

Gubin et al observed a higher mesor in young adults (97.5° F/36.38° C) than in elderly subjects (97.1° F/36.17° C); amplitude was also decreased in elderly subjects. The mean circadian acrophase was similar in both age groups (17:19 versus 16:93); however, inter-individual differences were higher in the older group, with individual values varying between 10:00 and 23:00 hours (Figure 4).[48]

Summary

The idea that normal body temperature of healthy adults is approximately 98.6° F/37.0° C is credited in large part to Wunderlich's observations. While his writings support this as a mean temperature in the population he monitored, it is important to realize that axillary temperatures were monitored exclusively, and there is uncertainty whether the thermometers he used were calibrated identically to those used today. More recent studies using thermometers with known calibration report significantly lower axillary and oral temperatures, with only rectal and gut temperatures approximating the mean values reported by Wunderlich. Available evidence indicates that site-specific means and ranges based on more recent clinical thermometry findings should be used in clinical settings.

A decision regarding which site to monitor should take into consideration available research findings. Core temperature appears to be best described by rectal temperature monitoring. Gut temperature accurately mimics rectal temperature in terms of acrophase, amplitude, mesor, and moment-to-moment changes, so is considered an accurate surrogate. Oral temperature also closely parallels rectal temperature in terms of amplitude, acrophase, and moment-to-moment changes; however, mesor and temperature range are shifted lower. While oral temperature also serves as an accurate surrogate for core-temperature changes over time, it typically provides a temperature value below actual core body temperature. When monitoring oral temperature, findings suggest it is important to monitor temperature at the posterior sublingual pocket to maximize reliability. Axillary and tympanic temperatures are considered less reliable since they do not as accurately parallel changes in rectal temperature. Evidence also suggests that axillary temperature can have very large side-to-side (left verse right axilla) variability, further weakening its reliability. Overall, data support using rectal, gut, or oral sites for monitoring temperature and using known site-specific reference ranges in interpretation of readings. Axillary and tympanic monitoring is not recommended, given the available research.

Two of the overlooked aspects of Wunderlich's writings are that normal temperature falls within a range of values, and temperature oscillates predictably with the time of day; these observations have been consistently verified. Thus, a healthy temperature at any site is described by a range of values, rather than a fixed value. This is important because when temperature is used to determine the relative health of an individual, a group mean will not necessarily accurately categorize an ideal temperature for all members of that group. Some healthy individuals would be expected to have values higher or lower than the mean and these values would, in theory, be normal for them.

Another conclusion from available findings is that the time of day when temperature is measured influences the range that would be considered normal for any given site. Time-of-day difference is critically important when monitoring temperature since it introduces a large and consistent source of variation. Available findings indicate that body temperature predictably reaches its lowest value during the

three hours prior to waking (03:00-06:00) and has a high value approximately 12-14 hours after waking. Failure to account for this healthy diurnal variation in temperature can lead to an erroneous conclusion that an individual's temperature, uncorrected for time of day, suggests a disease state when it is in fact a healthy temperature at that time of day.

The mean difference between the minimum and maximum temperature over any 24-hour period is expected to approximate 1.8° F/1.0° C in a large group of individuals. However, research suggests that, rather than any one temperature value in isolation, the degree of change of temperature over 24 hours might be a more important determinant of health in a given individual, with greater difference being consistent with better health. Two factors that can influence the degree of change are a person's relative physical fitness and age. In existing studies, greater fitness and younger age are characterized by larger temperature amplitudes, while poor fitness and advanced age are characterized by diminished amplitude. These findings (and other findings that will be discussed in part 2 of this review) suggest temperature amplitude might be a valuable assessment and could help categorize a person's relative health.

Body temperatures vary in a predictable manner throughout the menstrual cycle in a normally cycling female. The circadian rhythm of body temperature also persists throughout the menstrual cycle, so the menstrual cycle layers one rhythm on top of another existing rhythm. Although a circadian rhythm persists, it is notably different in the luteal phase. Naturally cycling women maintain a similarly shaped circadian body temperature curve in both the follicular and luteal phases; however, the entire curve is shifted upward by approximately 0.9° F /0.4° C in the luteal phase compared to the follicular phase. Although there is an upward shift in the waking, mean, and overall temperature curve, the difference between peak and trough values can decrease during the luteal phase. The decrease in amplitude occurs because the increase in trough value with ovulation is not accompanied by the same degree of increase in peak temperature value, resulting in a lessening of the difference between the two values. Menstrual variations in temperature should be considered prior to attempting to categorize a temperature (and its degree of diurnal change) as desirable or undesirable.

While several studies indicate time of year might significantly influence body temperature, available research does not allow for a definitive conclusion regarding this potential source of variability. Additional research is warranted to better categorize the seasonal rhythm of body temperature and to clarify existing contradictions.

Available evidence indicates that body temperature is a complex, non-linear variable, subject to many sources of endogenous and exogenous variation. This conclusion is apparent from the original work on clinical thermometry conducted by Wunderlich in the 1800s and equally if not more apparent in subsequent investigations of human body temperature.

The sources of variability discussed in this review affirm that variability is a defining characteristic of body temperature in healthy individuals. Ignoring this complex variability in favor of assuming that a single temperature defines health is an oversimplification of available research. To accurately extract meaning from any biological parameter, it is essential to understand and quantify how endogenous and exogenous sources of variability influence the data point being observed. Gaining a better understanding of sources of temperature variability, and using this understanding to interpret temperature results, is critical when temperature readings are used as a component of clinical decision making.

Part 2 of this review will analyze exogenous factors that influence body temperature and discuss information on body temperature findings in disease states.

References

1. Smolensky MH, D'Alonzo GE. Medical chronobiology: concepts and applications. *Am Rev Respir Dis* 1993;147:S2-S19.
2. Mackowiak PA, Worden G. Carl Reinhold August Wunderlich and the evolution of clinical thermometry. *Clin Inf Dis* 1994;18:458-467.
3. Wunderlich KRA. *Medical Thermometry and Human Temperature*. New York, NY: William Wood & Co.; 1871.
4. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA* 1992;268:1578-1580.

5. Wunderlich KRA. The course of temperature in disease: a guide to clinical thermometry. *Am J Med Sci* 1869;57:425-447.
6. Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. *Scand J Caring Sci* 2002;16:122-128.
7. Davy J. On the temperature of man. *Philos Trans R Soc Lond A* 1845;135:319-333.
8. Ogle W. On the diurnal variations of the temperature of the human body in health. *St George's Hosp Rep* 1866;1:221-245.
9. Moore RJ, Watts JT, Hood JA, Burritt DJ. Intra-oral temperature variation over 24 hours. *Eur J Orthod* 1999;21:249-261.
10. Rabinowitz RP, Cookson ST, Wasserman SS, Mackowiak PA. Effects of anatomic site, oral stimulation, and body position on estimates of body temperature. *Arch Intern Med* 1996;156:777-780.
11. Hamilos DL, Nutter D, Gershtenson J, et al. Core body temperature is normal in chronic fatigue syndrome. *Biol Psychiatry* 1998;43:293-302.
12. Agarwal N, Garg RK, Arora RC, et al. Oral versus axillary temperatures in human volunteers. *J Assoc Physicians India* 1990;38:541.
13. Edwards B, Waterhouse J, Reilly T, Atkinson G. A comparison of the suitabilities of rectal, gut, and insulated axilla temperatures for measurement of the circadian rhythm of core temperature in field studies. *Chronobiol Int* 2002;19:579-597.
14. Thomas KA, Burr R, Wang SY, et al. Axillary and thoracic skin temperatures poorly comparable to core body temperature circadian rhythm: results from 2 adult populations. *Biol Res Nurs* 2004;5:187-194.
15. Bogh M, Minors DS, Waterhouse JM. Can insulated skin temperature act as a substitute for rectal temperature when studying circadian rhythms? *Chronobiol Int* 1994;11:332-339.
16. Erickson R. Oral temperature differences in relation to thermometer and technique. *Nurs Res* 1980;29:157-164.
17. Singh V, Sharma A, Khandelwal R, Kothari K. Variation of axillary temperature and its correlation with oral temperature. *J Assoc Physicians India* 2000;48:898-900.
18. Refinetti R, Menaker M. The circadian rhythm of body temperature. *Physiol Behav* 1992;51:613-637.
19. Czeisler CA, Duffy JF, Shanahan TL, et al. Stability, precision, and near-24-hour period of the human circadian pacemaker. *Science* 1999;284:2177-2181.
20. Rivera-Coll A, Fuentes-Arderiu X, Diez-Noguera A. Circadian rhythmic variations in serum concentrations of clinically important lipids. *Clin Chem* 1994;40:1549-1553.
21. Waterhouse J, Weinert D, Minors D, et al. The effect of activity on the waking temperature rhythm in humans. *Chronobiol Int* 1999;16:343-357.
22. Van Someren EJ. More than a marker: interaction between the circadian regulation of temperature and sleep, age-related changes, and treatment possibilities. *Chronobiol Int* 2000;17:313-354.
23. Hanneman SK. Measuring circadian temperature rhythm. *Biol Res Nurs* 2001;2:236-248.
24. Sothern RB, Slover GP, Morris RW. Circannual and menstrual rhythm characteristics in manic episodes and body temperature. *Biol Psychiatry* 1993;33:194-203.
25. Carandente F, Angeli A, Crosignani P, et al. Circatrigintan rectal temperature and endocrine rhythms of clinically healthy, menstrually cycling women. *Prog Clin Biol Res* 1987;227B:533-548.
26. Baker FC, Waner JI, Vieira EF, et al. Sleep and 24 hour body temperatures: a comparison in young men, naturally cycling women, and women taking hormonal contraceptives. *J Physiol* 2001;530:565-574.
27. Nakayama K, Nakagawa T, Hiyama T, et al. Circadian changes in body temperature during the menstrual cycle of healthy adult females and patients suffering from premenstrual syndrome. *Int J Clin Pharmacol Res* 1997;17:155-164.
28. Coyne MD, Kesick CM, Doherty TJ, et al. Circadian rhythm changes in core temperature over the menstrual cycle: method for noninvasive monitoring. *Am J Physiol Regul Integr Comp Physiol* 2000;279:R1316-R1320.
29. Cagnacci A, Arangino S, Tuveri F, et al. Regulation of the 24h body temperature rhythm of women in luteal phase: role of gonadal steroids and prostaglandins. *Chronobiol Int* 2002;19:721-730.
30. Baker FC, Driver HS, Paiker J, et al. Acetaminophen does not affect 24-h body temperature or sleep in the luteal phase of the menstrual cycle. *J Appl Physiol* 2002;92:1684-1691.
31. Zuspan FP, Zuspan KJ. Ovulatory plasma amine (epinephrine and norepinephrine) surge in women. *Am J Obst Gynecol* 1973;117:654-661.
32. Little BC, Matta RJ, Zahn TP. Physiological and psychological effects of progesterone in man. *J Nerv Ment Dis* 1974;159:256-262.
33. de Mouzon J, Testart J, Lefevre B, et al. Time relationships between basal body temperature and ovulation or plasma progestins. *Fertil Steril* 1984;41:254-259.

34. Moghissi KS. Accuracy of basal body temperature for ovulation detection. *Fertil Steril* 1976;27:1415-1421.
35. Moghissi KS. Prediction and detection of ovulation. *Fertil Steril* 1980;34:89-98.
36. Buxton CL, Engle ET. Time of ovulation; a correlation between basal temperature, the appearance of the endometrium, and the appearance of the ovary. *Am J Obstet Gynecol* 1950;60:539-551.
37. McCarthy JJ Jr, Rockette HE. Prediction of ovulation with basal body temperature. *J Reprod Med* 1986;31:742-747.
38. Horne JA, Coyne I. Seasonal changes in the circadian variation of oral temperature during wakefulness. *Experientia* 1975;31:1296-1298.
39. Cisse F, Martineaud R, Martineaud JP. Circadian cycles of central temperature in hot climate in man. *Arch Int Physiol Biochim Biophys* 1991;99:155-159.
40. Kleitman N, Jackson DP. Body temperature and performance under different routines. *J Appl Physiol* 1950;3:309-328.
41. Honma K, Honma S, Kohsaka M, Fukuda N. Seasonal variation in the human circadian rhythm: dissociation between sleep and temperature rhythm. *Am J Physiol* 1992;262:R885-R891.
42. Levendosky AA, Josep-Vanderpool JR, Hardin T, et al. Core body temperature in patients with seasonal affective disorder and normal controls in summer and winter. *Biol Psychiatry* 1991;29:524-534.
43. Touitou Y, Reinberg A, Bogdan A, et al. Age-related changes in both circadian and seasonal rhythms of rectal temperature with special reference to senile dementia of Alzheimer type. *Gerontology* 1986;32:110-118.
44. Atkinson G, Coldwells A, Reilly T, Waterhouse J. A comparison of circadian rhythms in work performance between physically active and inactive subjects. *Ergonomics* 1993;36:273-281.
45. Mauvieux B, Gouthiere L, Sesboue B, Davenne D. A study comparing circadian rhythm and sleep quality of athletes and sedentary subjects engaged in night work. *Can J Appl Physiol* 2003;28:831-887. [Article in French]
46. Howell TH. Oral temperature range in old age. *Gerontol Clin (Basel)* 1975;17:133-136.
47. Mason DJ. Circadian rhythms of body temperature and activation and the well-being of older women. *Nurs Res* 1988;37:276-281.
48. Gubin DG, Gubin GD, Waterhouse J, Weinert D. The circadian body temperature rhythm in the elderly: effect of single daily melatonin dosing. *Chronobiol Int* 2006;23:639-658.