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# Do fever and anapyrexia exist? Analysis of set point-based definitions

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**Romanovsky, Andrej A.** Do fever and anapyrexia exist? Analysis of set point-based definitions. *Am J Physiol Regul Integr Comp Physiol* 287: R992–R995, 2004. First published June 24, 2004; 10.1152/ajpregu.00068.2004.—Fever and anapyrexia are the most studied thermoregulatory responses. They are defined as a body temperature ($T_b$) increase and decrease, respectively, occurring because of a shift in the set point (SP) and characterized by active defense of the new $T_b$. Although models of $T_b$ control with a single SP (whether obvious or hidden) have been criticized, the SP-based definitions have remained unchallenged. In this article, the SP-based definitions of fever and anapyrexia were subjected to two tests. In *test 1*, they were compared with experimental data on changes in thresholds for activation of different thermoeffectors. Changes in thresholds were found compatible with an SP increase in some (but not all) cases of fever. In all cases of what is called anapyrexia, its mechanism (dissociation of thresholds of different effectors) was found incompatible with a decrease in a single SP. In *test 2*, experimental data on the dependence of $T_b$ on ambient temperature ($T_a$) were analyzed. It was found that the febrile level of $T_b$ is defended in some (but not all) cases. However, strong dependence on $T_a$ was found in all cases of anapyrexia, which agrees with threshold dissociation but not with a decrease of the SP. It is concluded that fever (as defined) has only limited experimental support, whereas anapyrexia (as defined) does not exist. Two solutions are offered. A palliative is to accept that SP-based terms (anapyrexia, cryexia, regulated hypothermia, and such) are inadequate and should be abandoned. A radical solution is to transform all definitions based on comparing $T_b$ with the SP into definitions based on balancing active and passive processes of $T_b$ control.

thermoregulation; body temperature; febrile response; hypothermia; poikilothermy; thresholds; thermoeffectors; balance point

FEVER AND ANAPYREXIA are the two most studied thermoregulatory responses. Fever is caused by infectious, inflammatory, and other stimuli. In the laboratory, it is often studied by injecting animals with bacterial lipopolysaccharide (LPS) or mediators of its action: platelet-activating factor, pyrogenic cytokines (e.g., interleukin-1β and tumor necrosis factor-α), and prostaglandins of the E series (PGE). Fever is defined as an increase in deep body temperature ($T_b$) occurring because of an increase in the thermoregulatory set point (5, 6, 15). The inverse response, known as anapyrexia (5), cryexia (17), or regulated hypothermia (9), is commonly defined as a decrease in $T_b$ resulting from a decrease in the set point. It is thought to occur in injury, trauma, hypoxia, shock (e.g., LPS induced), heatstroke, intoxications (e.g., with ethanol), anesthesia, starvation, and other conditions.

The current definitions of fever and anapyrexia are based on a model of $T_b$ control requiring a single set point, either obvious (physiological) or hidden (mathematical). A physiological set point was used in many early models in which $T_b$ was compared with an independent signal (for review, see Refs. 14 and 41). Some more recent models [the most famous is one by Mitchell et al. (19)] involve comparing $T_b$- or heat flow-dependent signals with each other; these models can be described as having a mathematical set point. More than 20 years ago, Werner (41) demonstrated that all set point concepts are built on unnecessary and unproven assumptions, and that all of them represent special cases of a more general concept. Such a general concept is based on the balance of active (controlling) and passive (controlled) processes and requires neither a physiological nor mathematical set point. Similar concepts have become standard in several areas of neuroscience dealing with complex functions (23, 24). To accept Werner's concept would require transforming the current definitions of thermoregulatory responses: they should be based not on comparing $T_b$ with the set point but on determining at which value $T_b$ would balance in a given response. In many cases, such a fundamental transformation can be performed in a surprisingly simple way, i.e., by substituting the term set point with balance (or equilibrium) point. However, such a transformation has not happened. The set point-based definitions of fever and anapyrexia are assumed to work just fine and remain unchallenged dogmas.

In the present work, the validity of these definitions is questioned, and the definitions are subjected to a twofold analysis. First, it is analyzed whether these definitions agree with qualitative and quantitative experimental data on changes of thermoeffector activity. Second, the current definitions of fever and anapyrexia are used to derive a corollary that both responses should be insensitive to ambient temperature ($T_a$); this corollary is then checked against experimental data. The analysis shows that one of the two most studied thermoregulatory responses (anapyrexia) does not exist, whereas the other (fever) finds only limited experimental support. Two solutions are then offered: one attempting to alleviate this problem and the other to eliminate it.

## ANALYSIS

### *Test 1: Is the Activity of Thermoeffectors During Fever and Anapyrexia Compatible With Set Point Changes?*

*Qualitative approach.* During fever, $T_b$ typically rises as the result of coordinated behavioral (e.g., seeking a warmer environment) and autonomic responses; the autonomic responses involved are aimed at decreasing heat loss (e.g., skin vasoconstriction) and increasing heat production (e.g., activation of nonshivering thermogenesis in the brown adipose tissue; see Ref. 15). Similarly, it has been found in many (for review, see Refs. 9 and 34), but not all (18, 31, 37), cases of anapyrexia that the fall in $T_b$ is also achieved by coordinated behavioral (e.g., seeking a cooler environment) and autonomic responses; the autonomic responses involved are aimed at increasing heat

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loss (e.g., skin vasodilation) and decreasing heat production (e.g., inhibition of thermogenesis). In other words, both fever and anapyrexia can occur as the result of several effector responses all aimed at changing $T_b$ in the same direction. Such a qualitative approach is often used as proof that fever and anapyrexia can be adequately described as changes in the set point (e.g., Refs. 9, 15, 34). However, a quantitative approach produces different results.

*Quantitative approach.* The activity of each thermoregulatory effector is a function of $T_b$ (and other arguments). At a certain $T_b$, the effector is activated, and this threshold $T_b$ can be viewed as a $T_b$ value that this effector defends. As proposed by Satinoff (32), confirmed by solid experimental data (for review, see Ref. 22), and implied by analogy with other biological control systems (23, 24), effectors that form the thermoregulation system are largely independent. Therefore, when two thermoeffectors change their activity in what looks like a coordinated fashion (e.g., when skin vasodilation occurs simultaneously with inhibition of thermogenesis), they can still have different thresholds and defend different values of $T_b$. Hence, measurement of threshold $T_b$ values for activating effector responses (and not just thermoeffector activity) becomes a tool to probe the definitions of fever and anapyrexia. Figure 1 shows threshold $T_b$ values for two thermoeffectors, one representing cold-defense effectors ($T_{thr\text{-}cold}$) and the other representing heat-defense effectors ($T_{thr\text{-}heat}$). If fever and anapyrexia can be adequately described as an increase and a decrease (respectively) in a single thermoregulatory set point, as suggested by their definitions, experimental data should reveal parallel upward shifts of $T_{thr\text{-}cold}$ and $T_{thr\text{-}heat}$ in fever (Fig. 1*B*) and parallel downward shifts of $T_{thr\text{-}cold}$ and $T_{thr\text{-}heat}$ in anapyrexia (Fig. 1*C*).

The febrile response to LPS (and some other pyrogens) consists of at least three different phases (29), which are thought to be mediated differently (12) and have different thermoregulatory mechanisms (39, 40). When studying the second phase of LPS fever in rabbits, Vybíral et al. (40) found that $T_{thr\text{-}heat}$ (ear skin vasodilation) increases by 1.0°C (reaches 39.9°C), whereas $T_{thr\text{-}cold}$ (shivering) decreases by 1.5°C (reaches 37.4°C); such dissociated thresholds clearly contradict the set point definition of fever. However, the authors suggested (based on a literature analysis) that equal (or at least similar) shifts in $T_{thr\text{-}heat}$ and $T_{thr\text{-}cold}$ occur during the first phase of LPS fever. They later supported their suggestion by showing that $T_{thr\text{-}cold}$ (cold thermogenesis) increases during the first phase of LPS fever in rabbits by 1.0°C and by estimating that $T_{thr\text{-}heat}$ (vasodilation) shifts upward by a similar value (39). Szelényi et al. (38) obtained stronger support for the set point definition by measuring $T_{thr\text{-}heat}$ (tail skin vasodilation) and $T_{thr\text{-}cold}$ (thermogenesis) in rats and finding that both thresholds increase by the same value during PGE-induced fever.

Whereas it is plausible that equal upward shifts in $T_{thr\text{-}heat}$ and $T_{thr\text{-}cold}$ can take place during the first phase of LPS fever or during the response to PGE, equal (or even similar) downward shifts in $T_{thr\text{-}heat}$ and $T_{thr\text{-}cold}$ have not been found in any model of anapyrexia. In a rat model of LPS-induced shock (28) and a guinea pig model of heat disorder (25), $T_{thr\text{-}cold}$ (thermogenesis) drops by ~2°C, whereas $T_{thr\text{-}heat}$ (skin vasodilation) hardly changes. In a rat model of starvation, $T_{thr\text{-}cold}$ (thermogenesis) drops by almost 1°C, whereas $T_{thr\text{-}heat}$ (skin vasodilation) does not change (31). In a rat model of injury

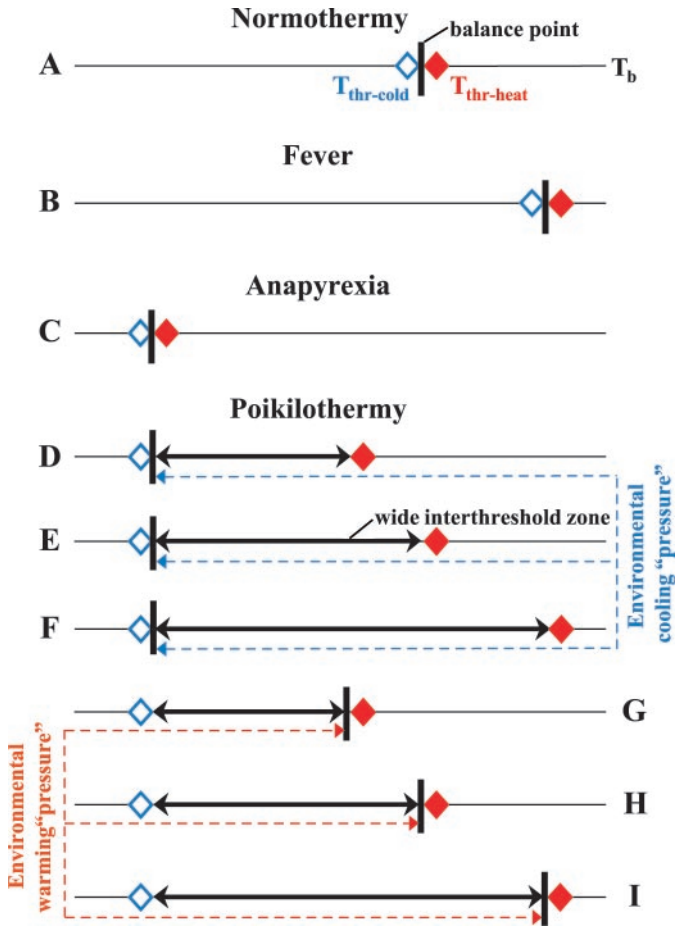


Fig. 1. Thermoregulatory strategies. The existence of normothermy (*A*), fever (*B*), and poikilothermy (*D–I*) is confirmed experimentally, whereas the existence of *strategy C* (anapyrexia) is not. For each strategy, the following points are plotted on the body temperature ($T_b$) axis: threshold $T_b$ for triggering cold-defense effectors ($T_{thr\text{-}cold}$), threshold $T_b$ for triggering heat-defense effectors ($T_{thr\text{-}heat}$), and balance point. The strategy presented in *D-I* is characterized by a large decrease in $T_{thr\text{-}cold}$ and one of the following positions of $T_{thr\text{-}heat}$: slightly decreased (*D* and *G*), unchanged (i.e., as in normothermy; *E* and *H*), or increased (*F* and *I*). When the environment cools the body (e.g., because of cold-seeking behavior), the balance point is always "pressed" down, toward $T_{thr\text{-}cold}$, and $T_b$ is always lower than normal, regardless of the position of $T_{thr\text{-}heat}$ (*D–F*). When the environment warms the body (e.g., because of warmth-seeking behavior), the balance point is pressed up, toward $T_{thr\text{-}heat}$. Depending on the position of $T_{thr\text{-}heat}$, this may result in lower than normal (*G*), normal (*H*), or increased (*I*) balance point and $T_b$. For simplicity, all cold-defense effectors are assumed to have the same threshold, $T_{thr\text{-}cold}$, and all heat-defense effectors are assumed to have the same threshold, $T_{thr\text{-}heat}$. Changes in the sensitivity of effector activity to $T_b$ are ignored. The nature of $T_b$ (see Ref. 41) is unrevealed. See text for explanations.

(limb ischemia), $T_{thr\text{-}cold}$ (shivering) decreases by a dramatic 4–5°C, whereas $T_{thr\text{-}heat}$ (tail vasodilation) does not decrease; on the contrary, it increases by ~1°C (37). Many studies in anesthetized humans show dissociation between $T_{thr\text{-}heat}$ and $T_{thr\text{-}cold}$ (for review, see Ref. 33). Indeed, opioids, intravenous anesthetics (e.g., propofol), and volatile anesthetics (e.g., isoflurane and desflurane) all decrease $T_{thr\text{-}cold}$ by several degrees Celsius, but they typically do not change $T_{thr\text{-}heat}$ and may even increase it. In other words, a large fall in $T_{thr\text{-}cold}$ is common in what is called anapyrexia, whereas a similar fall in $T_{thr\text{-}heat}$ does not occur. Even when a decrease in $T_{thr\text{-}heat}$ is relatively large [as in the studies by Borona and Gautier (4) and

Greif et al. (10)], it is still much smaller than the characteristic, several-degree decrease in $T_{thr\text{-}cold}$. The decrease in $T_{thr\text{-}heat}$ (thermal polypnea) seen by Borona and Gautier (4) in hypoxic cats was only 0.4°C, and it would be even several times smaller if the authors were to use a more conservative definition of $T_{thr\text{-}heat}$. In human volunteers treated with the opioid agonist nalbuphine (10), $T_{thr\text{-}heat}$ (sweating) decreased by 0.5°C, whereas the magnitude of the simultaneous decrease in $T_{thr\text{-}cold}$ (shivering) was more than two times larger.

*Test 2: Are Fever and Anapyrexia Independent of $T_a$?*

For both fever and anapyrexia, their set point-based definitions emphasize active defense of the new (increased in fever and decreased in anapyrexia) level of $T_b$ (6). Such a proposed defense should render these responses relatively insensitive to $T_a$. In the case of fever, data on the sensitivity of the response to $T_a$ are a mixed bag. On one hand, the same dose of LPS (13, 27, 30, 35) or platelet-activating factor (11) can increase $T_b$ at a near-neutral $T_a$ but cause at least a transient decrease in $T_b$ at a subneutral $T_a$. The ability to both increase and decrease $T_b$ has also been shown for "pyrogenic" cytokines interleukin-1β (20) and tumor necrosis factor-α (2) and is thought to reflect the dependence of the $T_b$ response on $T_a$ (20). On the other hand, there are data showing that the febrile level of $T_b$ during PGE fever is independent of $T_a$ (7, 36). In the case of anapyrexia, stimuli and conditions that are thought to cause this response (e.g., hypoxia, shock-inducing doses of LPS, severe heat, anesthesia, starvation) always produce responses characterized by a strong dependence on $T_a$: when $T_a$ is low, $T_b$ falls deeply; when $T_a$ is high, $T_b$ decreases slightly or not at all (3, 8, 28, 33, 42).

In summary, both *test 1* and *test 2* have shown that at least some (but definitely not all) fevers satisfy the set point definition, whereas every anapyretic response studied is incompatible with such a definition.

## SOLUTIONS

*Solution 1: A Palliative*

An easy solution would be to cease using the term anapyrexia and similar terms referring to a nonexistent phenomenon, a decrease in the set point. One can notice that the strategy shown in Fig. 1, *D–I*, represents exactly what happens with thermoeffector thresholds in the so-called anapyretic states (18, 25, 28, 31, 33, 37) and during the later phases of fever (40; also see *test 1* above). This strategy is characterized by a wide interthreshold zone formed by a drastically decreased $T_{thr\text{-}cold}$ at the low end and a slightly decreased (*D* and *G*), normal (*E* and *H*), or even increased (*F* and *I*) $T_{thr\text{-}heat}$ at the high end and represents the poikilothermic type of $T_b$ regulation (6). Within this wide interthreshold zone, $T_b$ is the result of passive heat transfer between the animal and the environment. It is no surprise, therefore, that this strategy is characterized by a strong dependence of $T_b$ on $T_a$. Such dependence has been repeatedly seen in "anapyretic" states (3, 28, 33, 42; also see *test 2*). When the environment is subthermoneutral (for definitions, see Ref. 26), the cooling pressure pushes the balance point (and $T_b$) down, toward $T_{thr\text{-}cold}$ (Fig. 1, *D–F*). A decrease in $T_b$ also occurs (and is especially efficient) when the poikilothermic type of thermoregulation is coupled with cold-seeking behavior. Activation of cold-seeking behavior and suppression of warmth-seeking behavior have been found in hypoxia, hemorrhagic shock, hyperosmolarity, LPS shock, and other anapyretic states (1, 9, 16, 28, 34). When the environment is suprathermoneutral, the warming pressure pushes the balance point (and $T_b$) up, toward $T_{thr\text{-}heat}$ (Fig. 1, *G–I*). If $T_{thr\text{-}heat}$ is elevated (as during LPS fever; see Ref. 40), $T_b$ increases (Fig. 1*I*). Such an increase is especially efficient when coupled with warmth-seeking behavior, which is typical during fever (15).

The poikilothermic type of $T_b$ regulation is widely spread in the animal kingdom (6). Phylogenetically, the vast majority of ectothermic animals are also bradymetabolic and poikilothermic; the transition to homeothermy (a feature of endothermic, tachymetabolic animals) is associated with the emergence of thermogenesis. There are also heterothermic animals that switch between poikilothermy and homeothermy; they do so by turning thermogenesis on and off. As a logical continuation, homeothermic animals use the same mechanism to decrease their $T_b$ during hibernation, REM sleep, starvation, hypoxia, shock, and intoxications: they shut down thermogenesis (drastically decrease $T_{thr\text{-}cold}$) and become poikilothermic. As suggested by Myers (21) for the thermoregulatory effect of alcohol, the term poikilothermy (not the set point-based anapyrexia or alike) should be used to describe thermoregulatory responses characterized by widening of the interthreshold zone.

*Solution 2: A Cure*

A more radical solution would be to transform all terms for thermophysiological responses so that they are based on balancing active and passive processes of $T_b$ control (41) rather than comparing $T_b$ with the set point. This would make fever a response in which $T_b$ balances above its normal value and anapyrexia a response in which $T_b$ balances below its normal value. The balance point-based definitions work for all cases where the set point-based definitions work (e.g., typical fever; Fig. 1*B*). Such definitions also work for all cases where the set point-based definitions do not work. For example, the dissociated changes in $T_{thr\text{-}cold}$ and $T_{thr\text{-}heat}$ seen in poikilothermy (Fig. 1, *D–I*) do not agree with a change of the thermoregulatory set point but readily agree with a change in the balance point, which has a definite position uniquely determined by $T_a$ and other environmental factors in a poikilothermic state. Four examples of positions at which $T_b$ can balance in poikilothermy are shown in Fig. 1: substantially below (*D–F*), slightly below (*G*), at (*H*), or above (*I*) the level of $T_b$ seen in normothermy (*A*). Figure 1 clearly shows how the same adjustment of the thermoregulatory system (the same set of $T_{thr\text{-}cold}$ and $T_{thr\text{-}heat}$) can result in drastically different $T_b$ values [compare, e.g., Fig. 1*F* and Fig. 1*I* corresponding to the later phases of the response to LPS (40)]. Such a difference is difficult to explain by using the set point-based definitions: how can the same shift in the set point represent both fever and anapyrexia at the same time, or how can the same shift in the set point result in either a decreased or an increased $T_b$?

For an experimenter, the balance point-based definitions are much more useful than set point-based definitions. Who has not seen a study in which a final conclusion is that the set point is increased or decreased under certain conditions? Such a conclusion is of no utility for understanding the regulatory mechanism (14, 41). It creates the illusion of understanding but

does not offer any mechanistic insight into what is happening with $T_b$ control: the single "command center" required to compare $T_b$ with the set point and to send specific "orders" to different effectors probably does not exist and, as such, cannot be studied. By eliminating the single set point (with all the underlying machinery), the balance point-based definitions draw attention to thermoeffector loops and passive elements of the system, i.e., to physiological and anatomic entities that exist and can be studied in direct experiments. For example, if a certain stimulus decreases the balance point of rat $T_b$, this stimulus most likely affects, directly or indirectly, the loop controlling thermogenesis in the brown fat, the major cold-defense effector in the rat. Hence, accepting *solution 2* not only gets rid of definitions that are experimentally unconfirmed (anapyrexia) or applicable only to specific cases (fever) but also dispels the illusion of understanding the thermoregulatory processes and opens them for exploration.

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