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The following is the abstract of the article discussed in the subsequent letter:

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.—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.

Comments on "Do fever and anapyrexia exist? Analysis of set point-based definitions"

To the Editor: Dr. Romanovsky's report (2) is a brave trial for falsifying the paradigm of the adjustable set point of temperature regulation. Courage in science is almost as precious as that on the battlefield. I greatly appreciate this effort. The author's reasoning, however, does not seem to be coherent enough and is not supported with a sufficient body of evidence. Dr. Romanovsky claims that "one of the two most studied thermoregulatory responses (anapyrexia) does not exist, whereas the other (fever) finds only limited experimental support" (2). His main argument is that during anapyrexia threshold body core temperature for thermogenesis decreases while that for skin vasodilation does not. He suggests that the resulting shift in core temperature strongly depends on ambient temperature, which makes an organism poikilothermic.

I think Dr. Romanovsky might be mistaken in two points: *1*) he seems to consider autonomic and behavioral thermoregulatory mechanisms not to be closely linked to each other, and *2*) he treats temperature regulation as a sovereign system.

Under appropriate laboratory conditions, thermal behavior, such as that displayed by an animal placed in a temperature gradient, allows the experimenter to identify clearly both anapyrexia (when a decrease in body temperature is coupled with cold-seeking behavior) and fever (when an increase in body temperature is coupled with warmth-seeking behavior). Therefore, Dr. Romanovsky's assumption that the "poikilothermic type of thermoregulation" coupled (accidentally?) with cold-seeking or with warmth-seeking behavior creates the illusion of anapyrexia or of fever (respectively) is obviously misleading. This kind of thermal behavior does not make an animal poikilothermic; on the contrary, it prevents poikilothermy, in both endothermic and ectothermic animals! Also the above-mentioned differences in thresholds for thermogenesis and skin vasodilation do not speak against the set point changes. Because the temperature regulatory system shares many organs with other regulatory systems, effector responses of the former, under conflict conditions, are compromised by various nonthermal disturbances. This was exactly the case in rats suffering from endotoxin shock (3). Skin vasodilation must have been then compromised by a profound drop in arterial blood pressure, recorded in that investigation. On the other hand, we (1) were able to show that cold-seeking behavior, displayed by rats exposed to endotoxin shock, allows them to develop an anapyretic drop in body temperature, which is highly likely to prevent neurotoxicity of the resulting cerebral ischemia. In contrast, skin vasodilation under such conditions would enhance the risk of cerebral ischemia. A similar cost-benefit relationship could be inferred from a modest decrease in the threshold of thermal polypnea in hypoxic cats, which was another example of the dissociation between thresholds for activation of thermogenesis and of heat loss presented in Dr. Romanovsky's paper (2). Such a context should also be taken into account in analysis of the opposite shifts in thermoregulatory set point, induced by various doses of bacterial lipopolysaccharide (1). In case of febrile response the priority is its antimicrobial (cytotoxic) effect, while anapyrexia is used for neuroprotection. Therefore, I cannot accept Dr. Romanovsky's final conclusion that using the paradigm of the adjustable set point "creates the illusion of understanding but does not offer any mechanistic insight into what is happening with T_b control" (2). I am sure it does offer a much deeper insight than applying Dr. Romanovsky's peculiar idea of "poikilothermic type of thermoregulation."

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REPLY

To the Editor: In his letter, Dr. Caputa concludes that the term set point "offers a much deeper insight" into deep body temperature (T_b) regulation than the term balance point (i.e., the value at which T_b would balance in a given state) proposed in my paper (7) and further developed in a recent review (8). We clearly disagree, and our disagreement with Caputa resembles a famous scientific dispute that was taking place several centuries ago. Interestingly, that dispute involved Nicolas Copernicus (1473–1543) after whom Caputa's university is named. From pre-Aristotelian times, the fact that celestial bodies keep certain positions in the sky and move in an orderly

fashion was explained with the help of crystal spheres, simple mechanical devices believed to hold stars and planets in their places. Supported with no experimental evidence, the term was repeatedly modified (by Copernicus among others) but eventually failed to keep up with the progress of science. When gravity was discovered, the crystal spheres were replaced with orbits (trajectories).

The story with the crystal spheres remarkably repeats itself in modern thermophysiology. The fact that T_b is regulated was explained with the help of an easily understandable engineering concept. According to this concept, thermal signals from different parts of the body come to the control center ("coordinator"), where they are integrated, the integrated signal is compared to a reference signal (set point), and an error signal is generated to drive thermoeffectors. Although no anatomic basis or physiological equivalent of the thermoregulatory set point was identified, the concept was kept alive with the help of various modifications, such as the adjustable nature of the set point reiterated by Caputa. No modifications, however, seem to be able to save this concept in view of the following achievements. First, due to the contributions of Satinoff, Kanosue, and others (2, 3, 6, 9), it has been established that thermoeffectors have largely independent circuitries; it has been further realized that their integration occurs not by a single command center, but mostly through the common controlled variable, T_b. Second, it has become clear that thermoeffectors function largely independently, and an impressive number of states where different effectors work to defend different levels of T_b have been identified (for review, see Ref. 7). Third, many examples of regulation without a single control center or set point have been found in various biological systems (1, 4, 5), and the fact that biological regulation differs drastically from engineering control has come to be recognized, in part due to the work of Partridge (4, 5). Finally, Werner (10, 11) has demonstrated that regulation of T_b can be explained based on the balance of active (controlling) and passive (controlled) processes, without a set point or single control center. Werner's balance model has the same implications for thermal physiology that the gravitational, crystal sphere-free model of planetary movement had for astrophysics.

In view of these developments, the term set point could continue to be used only if redefined as a balance point, but the intricate connection of the set point with the reference signal, coordinator, and other nonexistent machinery would invalidate such a new definition. Similarly, astronomers could have redefined the term crystal sphere as orbit and used it, but they elected not to; the intricate connections of the crystal spheres with nonexistent mechanical gadgets would have invalidated any clever definition. As was the case with the crystal spheres, the term set point should now give its place to a new name.

To support his conclusion, Caputa argues that the many experimental findings of dissociation of threshold T_bs for activation of cold- and heat-defense responses listed in my paper (7) are wrongly interpreted because the dissociation would allegedly disappear if two things were done: *1*) thermoregulatory behavior was included in the analysis, and *2*) any unwanted autonomic effectors were excluded from it. The first proposition (i.e., including thermoregulatory behavior) would not help Caputa's case. When two autonomic effectors have different thresholds (as in several studies cited in Ref. 7), it does not matter how many additional effectors are analyzed; the two dissociated thresholds will still remain dissociated. Furthermore, the effector that Caputa wants to add, thermoregulatory behavior, is actually a set of several distinct behaviors that themselves are controlled independently, without a single command center or set point (6). Dr. Caputa's second proposition, to exclude some autonomic effectors because of their supposed adaptive value and participation in other homeostatic processes, seems ungrounded.

The same proposition, however, can be viewed as a step in the right direction, because it admits that a single set point cannot explain the work of thermoeffectors, unless some of them are excluded from the analysis. The next step would be to get rid of the term set point and replace it with balance point. There is nothing to lose with such a replacement. Every true statement that contains the term set point will remain true if this term is changed to balance point, similar to how every piece of true knowledge obtained with the help of the crystal spheres (remember Copernicus' heliocentric system) remains true if the term orbits is used. What would be gained with such a replacement is the freedom from nonexistent gadgets and the ability to redirect scientific inquiry from the imaginary coordinator to the real active and passive elements of the thermoregulatory system.

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