# Rheostasis

## The Physiology of Change

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# Preface

Homeostasis has been a guiding principle in physiology for the last hundred years. That it has survived so well attests to its value. As a concept, however, homeostasis has received relatively little critical evaluation, despite Cannon having written that his account was "inadequate and provisional." There are, in fact, a number of considerations that are not adequately dealt with by current formulations of homeostasis. What happens, for instance, when the demands of two different regulatory systems clash? How can constancy of the *milieu intérieur* be maintained in such circumstances.

A point that is not generally appreciated is that the body does not always seek constancy of its internal environment. It does not always react in ways that prevent change. On the contrary, sometimes physiological mechanisms actively promote change. Specialists studying particular organs or systems have, of course, realized this. The scientific literature already contains numerous explanations couched in terms of changing set-points. One may read of the resetting of baroreceptors, osmostats, chemostats, and alphastats. Adjustments to thermostats, gonadostats, mechanostats and lipostats have already been proposed. But some name is needed to recognize the generality of these phenomena. Rheostasis is a convenient term for designating changes in regulated levels.

Changes in regulated levels have often initially been regarded as failures of homeostasis. Only later has the adaptive value of some of these changes been discerned. Keeping the internal environment constant is not always an overriding imperative.

This book is a reexamination and elaboration of the concept of homeostasis to include changes in regulated levels, rheostasis. Its main chapters collate, compare, and categorize examples of rheostasis for a variety of physiological variables. Conflicts between different regulatory systems emerge as a common circumstance promoting rheostasis, but too little is known about changes in regulated levels to sketch in more than a few rudiments. It is hoped, nevertheless, that an attempt to look at homeostasis from a more evolutionary perspec-

tive and to elaborate on what is already a very useful concept may constitute a small step toward establishing some valid principles. If even that is too ambitious, then perhaps at least some readers will share the pleasure of comparing the physiology of change in apparently disparate phenomena.

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# Contents

# Rheostasis

# 1

# Homeostasis Reexamined

The concept of homeostasis has become so familiar to biologists today that sometimes they fail to appreciate its splendor, like a fine picture that goes unnoticed because it hangs in the same position on the wall from day to day. But if we pause to look again, we find that the themes that inspired Claude Bernard and Walter Cannon are as universal as ever. Here we are, on this earth, composed of matter that is extraordinarily unstable. It takes only a few minutes of oxygen deprivation before our neurones are irreparably damaged, and a rise in body temperature of only a few degrees centigrade before our proteins begin to denature. Compared with all the cosmic forces that swirl around us, our bodies seem extremely fragile.

What Bernard realized was that the hostile forces outside of us are only part of our environment because we also have an internal environment, the friendly *milieu intérieur.* Numerous physiological reactions maintain stability in this milieu, and we manage to survive despite our mechanical and chemical fragility—and not merely survive, but to survive in a way that enables us to disregard the external environment most of the time. According to Bernard, *"La fixité du milieu intérieur est la condition de la vie libre."* Here *libre* means independent. By maintaining constancy in the internal environment, we free ourselves of constraints from the external environment; we can live in the desert, in the Arctic, even in outer space. Space travel is the ultimate example of homeostasis, because inside the space vehicle, inside the helmet and the space suit, inside the skin, you find the same old *milieu intérieur,* 37°C, 90 mg sugar/dl blood, the same old plasma calcium and potassium concentrations. Much of the technical elaboration that permits space travel has the same purpose as our terrestrial physiologies—to maintain stability in the internal environment. As Bernard (1878) put it, "all the vital mechanisms, however varied they may be, have but one end, that of preserving constancy in the internal environment."

If we go back to Bernard and Cannon, we find a freshness and breadth of vision that are often lacking today. But we too have our strengths. Among the advantages of intense specialization are deepening analysis of the details and the acquisition of major data bases. How do these two approaches fit together?

More specifically, how does the sweeping concept of homeostasis stand up in the light of recent facts? That homeostasis has received so little critical examination attests to its incontestable value in making sense of the facts. Yet at the end of his 1929 paper, Cannon said that errors had probably crept in, that his review was "inadequate and provisional," the start of a process rather than a conclusive statement. "In such a venture . . . crude ideas are sure to be projected which must later be refined." It is a tribute to Cannon rather than a criticism to take up this challenge. And when we look closely again at the magnificent panorama of homeostasis we find that it contains unconvincing passages, erroneous depiction, and some dubious coloring.

Before we consider these inadequacies, it needs to be said that there are several views of homeostasis, with somewhat differing emphasis. There is Bernard's original statement, with constancy of the *milieu intérieur* as its centerpiece. There is Cannon's elaboration, with more emphasis on dynamic equilibria and variability. He picked the word hom*eo*stasis rather than homo-stasis to indicate similarity, with some variability, rather than sameness. Then comes a newer view: homeostasis is equated with the operation of negative feedback systems. How entrenched this view has become is illustrated by a quotation from a short exposition (Langley, 1965) of homeostasis for undergraduates:

> Cannon's word, *homeostasis* embraces the fixed, or constant, internal environment, but then goes on to suggest dynamic, self-regulating processes that serve to maintain that constancy or to return the internal environment to normal should it get out of whack. This is the concept now referred to as *negative feedback,* that is, if there is a deviation in one direction, there is a reaction in the opposite direction.

Another example comes from Guyton's (1982) textbook.

> The term *homeostasis* is used by physiologists to mean *maintenance of static,* or *constant, conditions in the internal environment.* Essentially all the organs and tissues of the body perform functions that help maintain these constant conditions. . . .
>
> In this mechanism [baroreceptor pressure-regulating mechanism], it is clear that a high pressure causes a series of reactions that promote a lowered pressure, or a low pressure causes a series of reactions that promote an elevated pressure. In both instances these effects are opposite to, or *negative* to, the initiating stimulus, hence the term "negative feedback."
>
> Essentially all other control mechanisms of the body also operate by the process of negative feedback.

There follows here a list of limitations in these various accounts of homeostasis. This list starts with several sections that illustrate why homeostasis should not be equated with negative feedback. It then broadens to consider the lack of evolutionary perspective in early formulations of homeostasis and the failure to encompass changes in defended levels. For many readers these cautions about simplified views of homeostasis will be gratuitous. For those who have not had time to think about the subject they may be helpful.

## FEEDFORWARD

It has been realized, especially by McFarland (1970, 1985) that homeostasis does not depend exclusively on feedback; it also involves feedforward. "The term *feedforward* is used for situations in which the feedback consequences of behavior are anticipated and appropriate action is taken to forestall deviations in physiological state" (McFarland, 1985). Although little is known about the actual mechanisms involved, feedforward is not uncommon. For instance, eating usually has osmotic consequences, with salt and other nutrients producing dehydration. Much of a rat's water intake occurs in association with its meals; fine-grain analysis reveals that this prandial drinking takes place mostly before the meal or during the first 30 seconds of the meal, that is too soon for the full osmotic effects of the food to be felt (Kissileff, 1969). Water is also used for evaporative cooling by the thermoregulatory system. Pin-tailed sand grouse, *Pterocles alchata,* in parts of Morocco where air temperatures can reach 50°C, forage for water in the early, cooler parts of the day. This avoids having to fly (and the associated higher metabolic rate) during the intense heat of the middle of the day. Drinking controlled by feedback mechanisms would be more likely to occur during or after the hottest times of day. The early morning flights to water sources seem more likely to be controlled by feedforward mechanisms (Thomas and Robin, 1977).

A good way to appreciate the difference between feedback and feedforward is to note, as in Figure 1–1, that sensors can be made to detect changes in either the regulated variable or in disturbances that affect that variable (Houk, 1980). When the sensors are responsive to the value of the regulated

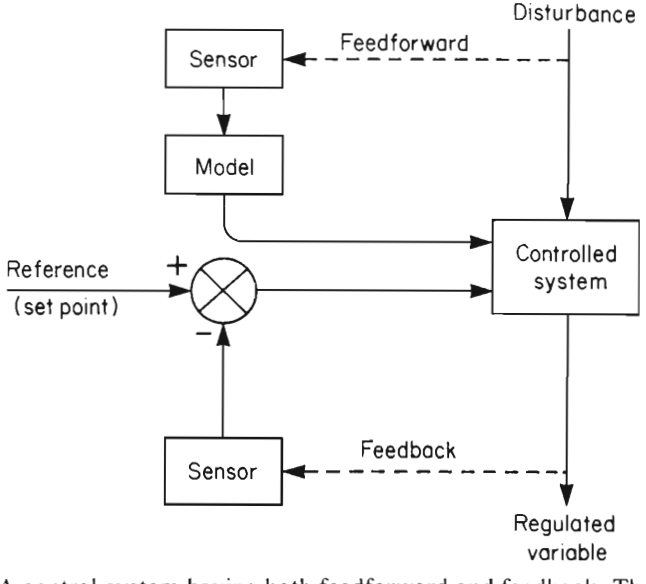



**Figure 1–1.** A control system having both feedforward and feedback. The feedforward is shown influencing the controlled system, but it might exert its effects at some other point (Houk, 1988). For further explanation, see text.

variable, this is called feedback; when the sensors are responsive to the disturbances, this is called feedforward. For feedforward to be useful, the system must in essence contain a model of how the regulated variable will respond to disturbance. Such models are probably complex and should be modifiable by learning (Houk, 1980). For instance, the traditional view that tolerance to drugs depends on compensatory feedback mechanisms is being supplemented by the realization that feedforward contributes through the Pavlovian conditioning of responses that oppose and attenuate the effects of the drugs (Siegel et al., 1987). When these anticipatory responses are elicited without the drug itself being given, withdrawal symptoms appear.

Feedforward and feedback are not mutually exclusive: they can operate alongside each other, as an experiment on doves illustrates (Fig. 1–2). When offered water after 48 hours of deprivation the birds started to drink, presumably in reaction to feedback signals indicating deficits, but the amounts taken were greater if the birds were put in a warm environment for the test. The doves drank in one draught soon after being given access to water. The greater drinking at warm temperatures anticipated the threat of thermally induced dehydration. It is therefore an example of feedforward (Budgell, 1970).

## POSITIVE FEEDBACK AND RESPONSE MOMENTUM

A variety of activities are necessary for an animal's well-being. For instance, a rat needs to groom, sleep, eat, drink, find a mate, and build a nest. If behaviors were initiated as soon as a deficit occurred and terminated as soon as a deficit was abolished, there would be much switching between different activities (de Ruiter and Wiepkema, 1969; McFarland, 1971). A few mouthfuls of food would be enough to eliminate hunger and the animal would then start to do something else. But because it had ingested so little, this other activity would soon be interrupted by another bout of feeding. Such dithering could be energetically wasteful, especially if the food source were far from the home or from the site where other activities occurred. One way to make the rat into a meal eater rather than a nibbler, to maintain response momentum, is positive feedback (Wiepkema, 1971).

The efficacy of appetizers probably depends on positive feedback. The

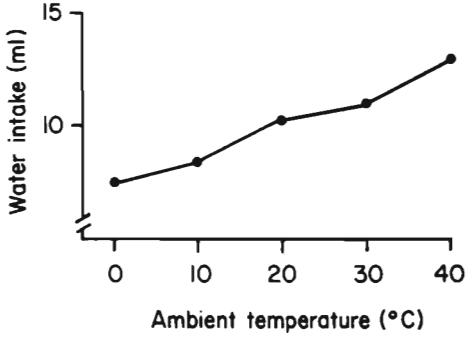



**Figure 1–2.** Water intake of doves, after 48 hours without drinking, during short tests conducted at different ambient temperatures (adapted from Budgell, 1970).

subject has been well studied in mice (de Ruiter and Wiepkema, 1969; Wiepkema, 1971). When rodents take a meal, they do not eat continuously but pause between bouts of chewing. In a previously food-deprived mouse these pauses are less frequent and the chewing bouts longer than in an animal at its normal weight. The animal therefore ingests more in a given time. This information about meal structure in a hungry animal helps in interpreting the behavior of a mouse fed *ad libitum*. In the latter the speed of eating increases at the start of a meal. Rather than slowing down and pausing more as more food is taken in, initially the mouse does the opposite and acts as if eating makes it still hungrier. The accelerated ingestion at the start of the meal depends on stimulation from the taste receptors because it is abolished if the food is made unpalatably bitter. Eventually, of course, feeding slackens and stops as the animal becomes fuller, but at first it behaves as if there were a positive feedback. Whether the phenomenon actually depends on a positive feedback loop, say some recurrent collaterals coming back to and stimulating their neurones of origin, or on inhibition of some other system that normally inhibits eating, is an open question (de Ruiter and Wiepkema, 1969). In either case response momentum is maintained.

Another example of response momentum that is hard to explain without invoking something in addition to negative feedback occurs after glucoprivation. It is possible to make rats eat more than usual by injecting insulin in doses sufficient to lower blood sugar levels to values of about 50 mg/dl. But if rats are prevented from feeding for 6 hours their blood sugar climbs back to the same level measured in saline-injected controls, presumably as a result of gluconeogenesis from liver glycogen or by other physiological means. Remarkably, if food is then offered, the rats eat more than the controls, even though the glucose level is now the same in the two groups (Ritter et al., 1978). Even when plasma glucose levels are raised to just above normal by infusing glucose toward the end of the 6 hours without food, the insulin-injected animals eat more than controls that had not been given insulin earlier. Perhaps once the commands for defense have been launched there is some obligatory delay before they can be rescinded, or perhaps the feeding is in response to some secondary metabolic change that results from temporary glucoprivation (see also Nonavinakere and Ritter, 1983). Whatever the underlying mechanism, it is clear that although severe glucoprivation is a way to increase feeding, the glucoprivation does not actually have to be present when the hyperphagia occurs.

A continuing response in the absence of a deficit has also been described in the Pekin duck after challenges with osmotic stimuli (Hammel, 1989). Infusions of hypertonic NaCl solutions stimulate the nasal salt gland to become active. However, once triggered, the gland continues to excrete salt at a greater rate than the sodium chloride is infused. This drives the tonicity of the blood down to levels that are actually lower than those needed to trigger the excretory response in the first place. Why does the response outlast the osmotic stress? One possibility that should be considered in such cases is that there is a negative feedback system but with integral rather than proportional control. In integral control the response strength of the effectors depends not only on the discrepancy between the actual and the set value of the defended variable but

also on how long the actual value has been displaced from the set-point (Hardy, 1961). In the case of the Pekin duck, integral control was not supported by experiments in which the rate of infusion was varied. Therefore, a positive feedback loop was suggested as a possible explanation of the continued response.

## CRISIS AND NORMAL BEHAVIOR

In discussing the increased speed of ingestion at the start of a meal in the mouse, we assumed that initially there is a deficit and that positive feedback maintains the restorative responses once they have begun. Even this, in some cases, may give too much prominence to deficit correction in the control of behavior. For example, it is not clear that there usually is a deficit when a mouse or rat starts to eat. There is always some food in the stomach of a rat when it has *ad libitum* access to food in the laboratory (Collier et al., 1972; Armstrong et al., 1978), yet it takes a number of discrete meals throughout the course of each day. This number is greatly influenced by the environmental conditions. If the rat must work to obtain a meal, then it takes fewer but larger meals (Collier et al., 1972). The animal adjusts its behavior within a few days each time the work requirement is altered. The strong and relatively rapid influence of environmental conditions suggests that, in a rat at normal body weight, internal energy deficits are relatively unimportant in the control of meal patterns. Before dismissing a depletion–repletion account of feeding in the undeprived animal, there should be a detailed examination of the behavior immediately after schedules are changed, that is before the internal milieu could alter. However, there is already a good case for thinking that the animal acts as an economist would, surveying the distribution of resources in the environment and the costs in obtaining them. It then arranges its patterns of exploitation so that it obtains these resources at the optimum time and rate. Its foraging behavior is not closely governed by any feedback from the *milieu intérieur* (Collier, 1985, 1986).

Of course, meal-taking behavior contributes toward preserving a stable *milieu intérieur* over the long term. Influences from the outside environment on eating patterns do not replace homeostasis. For example, even when the rat has to press a bar 80 times for each meal and takes only a few meals during the day, it still manages to maintain its body weight (Collier et al., 1972). Homeostatic defenses against becoming too fat are also evident despite environmental influences. When a satiated rat is induced to eat more than it ordinarily would at a particular time of day by being presented with a stimulus that has been associated with eating, the animal compensates for the conditioned eating by taking less food later in the day (Weingarten, 1984). Over a 24-hour period, food intake remains relatively constant despite different meal patterns. Environmental constraints on feeding are not, therefore, a negation of homeostasis. They suggest rather that homeostasis is taking a longer-term perspective and the animals are not constantly "riding a roller coaster of energy balance from

the heights of repletion to the depths of depletion" (Weingarten, 1985). In fact, by taking environmental constraints into account, and by eating again before nutrients are emptied from the stomach, the rat is probably able to keep the *milieu intérieur* more stable than would be possible by reactions to signal errors in a simple negative feedback system.

Should some crisis arise, responses to deficits are available, even though they are not normally called upon. More is eaten after glucoprivation, but the blood sugar level must be driven down to near 50 mg/dl to obtain the effect. This is far below the normal levels that occur during intermeal intervals. Moreover, at 50 mg/dl rats become ataxic and show other signs of neurological impairment (Brandes, 1977). It would hardly be adaptive for an animal to start eating only when reduced to this state. It must be said, however, that small drops in blood sugar (about 10%) have been detected just prior to a meal (Louis-Sylvestre and Le Magnen, 1980; Campfield et al., 1985). It is debatable whether these are the primary cause of subsequent eating or the result of hormonal changes (e.g., an anticipatory increase in insulin) that occur once a decision has been taken to initiate a meal shortly. Certainly glucoprivation is not necessary for normal feeding. It has long been recognized that lateral hypothalamic lesions can abolish the feeding response to insulin-induced hypoglycemia but that the lesioned animals still eat meals and respond to food deprivation and changes in environmental temperatures. Glucoprivic control of feeding probably "functions only during emergencies to reverse large and life-threatening decreases in blood sugar" (Epstein et al., 1975).

This discussion of blood sugar and feeding illustrates the general point that behaviors contributing to overall homeostasis need not be driven by discrepancies between actual and set values or by persistent load errors in a negative feedback system. They may result from anticipation, positive feedback, and economic planning over a longer time span in a way that prevents deficits from developing.

In a similar way, breathing is not always driven by rising and falling levels of $CO_2$ in the blood. During wakefulness some nonchemoreceptor input to the respiratory center keeps $CO_2$ below levels that stimulate breathing (see Sullivan, 1980). Should the $P_{CO_2}$ rise much above 40 mm Hg—for example during exercise or some emergency—central $CO_2$-sensitive chemoreceptors in the ventral medulla are ready to boost minute volume (respiratory rate $\times$ tidal volume). In more extreme situations peripheral $O_2$-sensitive chemoreceptors in the carotid and aortic bodies come into action. But chemoreceptors are not essential for breathing to occur. This is evident from a consideration of the affliction known as Ondine's curse, in which minute volume fails to increase in response to elevated $P_{CO_2}$, in some cases even when $P_{CO_2}$ rises above 60 mm Hg (e.g., Shannon et al., 1976). Yet during the awake state breathing continues in a relatively normal way, driven presumably by some neural input rather than by the chemoreceptors. However, in slow wave sleep breathing fails, the neural input to the respiratory centers evidently being inhibited in this state and the chemoreceptive system remaining deficient (Shannon et al., 1976).

## DIFFERENT MECHANISMS FOR CONSTANCY

The existence of behaviors that prevent internal instabilities from developing is only one illustration of the inappropriateness of equating homeostasis with any single type of mechanism. Another is that, even without feedforward, defense of stable levels could be achieved in a variety of ways. One is to compare the value of the feedback against that of a reference signal, or set-point, as shown in the most commonly given type of diagrams (Fig. 1–3). In this case there is a set-point in the strict engineering sense of the word.

It is also possible to generate stability and defense by having two opposing systems balancing each other out at a particular level (Fig. 1–4). For instance, constancy of temperature might arise through inputs from cold and warm detectors activating heat gain and heat loss responses, respectively. The more the heat gain responses were stimulated, the higher the temperature would be driven, but also the more the heat loss responses would be activated. With proportional control, a point of balance would then arise between the opposing systems, the exact level depending on the activation thresholds and proportionality constants for the heat gain and heat loss. A change either in the threshold or in the proportionality constant (slope of the lines in Figure 1–4) would alter the point of balance (Mitchell et al., 1970).

Such a system has no reference signal in the engineering sense, but it still behaves as if there were an engineer's set-point. The term *set-point* may therefore be used in a descriptive way. Houdas and Guieu (1975) have distinguished between descriptive and explanatory models. The former "represent the experimental observations without assuming the structure of the controller." Also Bligh (1975), considering certain temperature changes, concludes, "we can only say that it is *as if* a set-point has been changed." Set-point has also

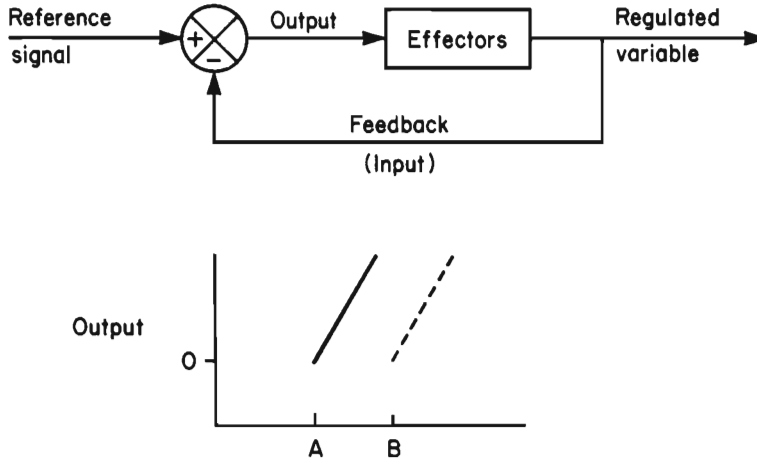



**Figure 1–3.** Top: control system employing a reference signal/set-point for regulating the level of a variable. Bottom: input–output relationships showing that the regulated level shifts (dotted line) from A to B when the value of the reference signal is raised (adapted from Mitchell et al., 1970).

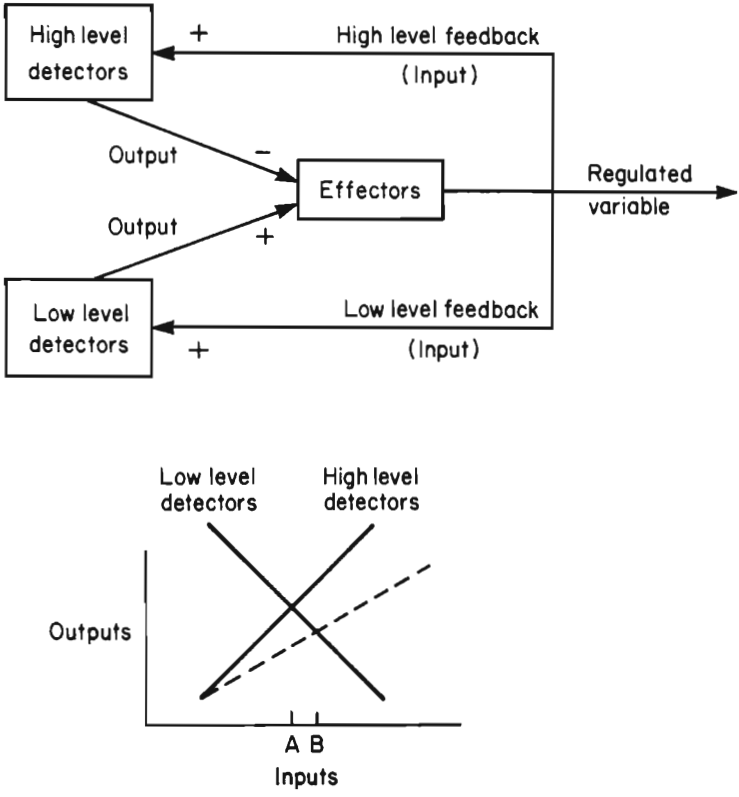



**Figure 1–4.** Top: a control system for regulating the level of a variable without employing a reference signal/set-point. Bottom: input–output relationships showing that when the gain of the high-level detectors is reduced (dotted line) the regulated level changes from A to B (adapted from Mitchell et al., 1970). In this book changes in the slope of this kind are referred to as changes in responsiveness.

been applied in this way to body weight regulation (Mrosovsky and Powley, 1977). This is the way it will be used in this book, as a convenient descriptive term without implying a particular control system.

It is sometimes possible in particular cases to distinguish experimentally between the control systems shown in Figures 1–3 and 1–4 (Mitchell et al., 1970; Cabanac and Massonnet, 1974; Mrosovsky and Powley, 1977), but it is not especially easy. In many situations the two systems behave in similar ways. All the more reason for emphasizing that homeostasis need not depend on a particular kind of mechanism.

## LACK OF EVOLUTIONARY PERSPECTIVE

The fathers of the concept of homeostasis were physiologists. For them, evolution it seems, was linear. Cold-blooded animals were seen as "much less highly organized" (Cannon, 1939), not having attained the controlled internal

environment of birds and mammals. That reptiles could be just as highly specialized for particular niches and for reproducing successfully was foreign to this way of thinking. "All the vital mechanisms," said Bernard, "however varied they may be, have but one end, that of preserving constancy in the internal environment." He did not discuss the possibility that reproductive output might be a higher and overriding end.

Constancy of the internal environment provided independence from the external environment. For Cannon this freedom *from* the external environment implied freedom *for* something else. His remarks when trying to answer the question "freedom for what?" are particularly revealing:

> It is chiefly freedom for the activity of the higher levels of the nervous system and the muscles which they govern. By means of the cerebral cortex we have all our intelligent relations to the world about us. By means of it we analyze experience, we move from place to place, we build airplanes and temples, we paint pictures and write poetry, or we carry on scientific researches and make inventions, we recognize and converse with friends, educate the young, express our sympathy, tell our love—indeed, by means of it we conduct ourselves as human beings. The alternative to this freedom would be either submission to the checks and hindrances which external cold or internal heat or disturbance of any other constants of the fluid matrix would impose upon us; or, on the other hand, such conscious attention to storage of materials and to altering the rate of bodily processes, in order to preserve constancy, that time for other affairs would be lacking. It would be like limiting social activities because of domestic duties. . . ."
>
> Cannon (1939)

Homeostasis was for poetry rather than for producing grandchildren—that would border on the domestic. Why some of the less poetic lower mammals should have equally effective homeostasis is not explained. Views similar to those of Cannon were put forward by Barcroft (1932). He was impressed by the breakdown of his mental abilities—the first to suffer—in experiments that severely challenged his homeostatic systems. From these experiences and other evidence he argued that the CNS, especially its higher functions, were the chief beneficiaries of a constant internal environment. The *vie libre* was, essentially, a matter of intellectual ascendancy.

Lack of modern evolutionary perspective and the absence of terms like *reproductive fitness* do not detract from Bernard's and Cannon's luminous insights into physiology. But their focus on physiological mechanisms for maintaining constancy may help explain their attitudes when confronted with examples in the animal kingdom of variation in the *milieu intérieur.* Those attitudes are outlined in the next section.

## CHANGES IN DEFENDED LEVELS

Cannon (1929) appreciated that the fluid matrix was not completely constant but he thought that variations were normally kept within narrow limits. He did not consider the possibility that the internal environment might change but still be homeostatically defended, nor did he cover the topic of biological rhythms.

Bernard talked of *la vie oscillante* but not so much as a description of rhythms as of cases in which the organism's functioning depended greatly on external conditions. Bernard considered mammalian hibernators as examples of *la vie oscillante,* along with plants:

> Tous les végétaux sont dans ce cas. . . . Tous les invertébrés et, parmi les vertébrés, tous les animaux à sang froid, possèdent une vie *oscillante, dépendante* du milieu cosmique. Le froid les engourdit, et si pendant l'hiver ils ne peuvent être soustraits à son influence, la vie s'atténue, la respiration se ralentit, la digestion se suspend, les mouvements deviennent faible ou nuls. Chez les mammifères, cet état est appelé *état d'hibernation*: la marmotte, le loir nous en fournissent des exemples. . . . Il y a absence, chez l'animal à sang froid ou hibernant, d'un mécanisme qui maintienne autour des éléments un milieu constant en dépit des variations atmosphériques.
>
> Bernard (1878)

We now know that when hibernators become torpid it is not because they are overcome by cold, but because they are regulating their temperatures at lower levels. This will be discussed in Chapter 4, along with numerous other examples of changes in defended levels. A change in the defended level of the internal environment is an elaboration, not a contradiction, of homeostasis. It is sufficiently common, however, and it has enough ramifications to merit its own name, rheostasis, the principal topic of this book.

## COMPETITION BETWEEN DIFFERENT REGULATORY SYSTEMS

What happens when the demands of different regulatory systems clash? Physiologists working in laboratories usually do not encounter this problem. It may never arise if conditions are standardized and only one variable manipulated at a time. Even when the whole animal is studied, as in Richter's (1943) classic demonstrations of behavior as a way of regulating the internal environment, the experiments usually adhere to a design with a single independent variable. The animal is provided with all its needs except one, the compensatory mechanisms for the deficiency are recorded, and another affirmation of homeostasis is obtained.

Outside the laboratory things may look different. Observations on Merino sheep illustrate the contrast. The body temperature of these animals in the laboratory seldom exceeds 39.5°C; if it does go higher, then shallow panting-type respiration ensues. But when sheep of this breed were fitted with telemetry equipment and allowed loose in a field, body temperatures often rose above 40°C, even above 41°C on occasions; this was in Australia in March (Brown, 1971). Despite these high temperatures, panting was not seen. Outdoors, the upper limits of body temperature were more variable and less well defended than indoors. In this case, it is not obvious why the animals should not maintain stable temperatures when outside.

In other examples the reasons for abandoning stability are evident. Camels *(Camelus dromedarius)* live in an environment that is both dry and hot. They are too large to rely on behavior to keep cool; they cannot burrow into the sand

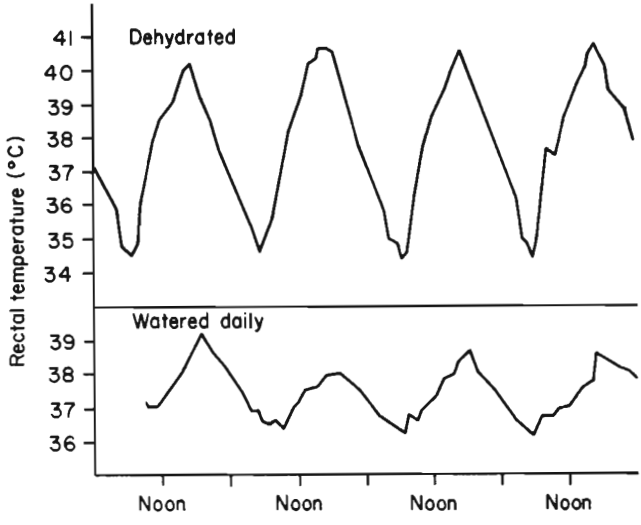



**Figure 1–5.** Diurnal changes in the rectal temperature of a camel. (Based on Schmidt-Nielsen et al., 1957, adapted from Schmidt-Nielsen, 1964, *Desert Animals: Physiological problems of heat and water.* Oxford University Press.)

or always find shade. The only other means at their disposal is evaporative cooling, but this uses water. The demands of water balance and thermoregulation clash. The camel solves the dilemma by allowing its temperature to rise during the day to levels that would be considered hyperthermic in most mammals (Fig. 1–5). This saves water. The extent of the daily temperature rise depends on the premium placed on water conservation: it is greater if the animal is dehydrated. At night the body temperature falls below mammalian norms, sometimes dropping as low as 34.2°C. This cooling delays the time when dangerously high temperatures will be reached the next day as the camel warms up (Schmidt-Nielsen et al., 1957).

Recently physiologists have been paying more attention to interactions between regulatory systems. For example, a book on thermal physiology (Hales, 1984) devotes a whole section to competition between thermoregulation and other homeostatic systems.

## SUMMARY

In a single example, the camel's physiology illustrates many of the principal limitations to the simple concept of homeostasis.

1. Nocturnal hypothermia anticipates the next day's heat; it represents a type of feedforward mechanism.
2. Although temperature is not constant, it is defended (the evidence for this last statement is given in Chapter 5). The animal is not entirely at the mercy of the environment, even though its temperature oscillates with it.

3. The lack of stability in the *milieu intérieur* does not represent a primitive stage in evolution: it is a specialized adaptation.
4. Lack of stability arises out of competition between two regulatory systems, a situation not discussed by Bernard or Cannon.

## PREVIEW

Rheostasis of one variable is not the only way of resolving conflicts between the demands of different regulatory systems. Therefore, before describing numerous examples of rheostasis (the core of this book in Chapters 4 and 5), it may be illuminating to consider next (in Chapter 2) what other possibilities exist for conflict resolution. This may help provide some appreciation of the circumstances in which rheostasis is likely to evolve.

# 2

# Resolving Conflicts

The appropriateness of calling rheostasis into action when conflicts occur depends on what other options there are for settling matters. Some possibilities are introduced in the sections that follow through examples of conflicts that have deliberately been arranged and studied.

## SWITCHING EFFECTOR MECHANISMS

Johnson and Cabanac (1982a) studied rats in a laboratory environment consisting of a "home" with access to a "restaurant." The home was warm (25°C) but had no food in it. The restaurant was open for 2 hours a day; it was 2 m away from the home and it was cold, very cold (−15°C). The menu was limited to powdered food to prevent hoarding. The experimenters wanted to find out whether rats in this situation would eat less than normal or whether they would get cold. The answer was neither. The rats outwitted the experimenters, but in an instructive way. They did two things that enabled them to eat enough in a cold restaurant without themselves becoming hypothermic. They ate faster and they sat on the base of their tails and bodies, with their back feet off the ground, so that their unfurred extremities were off the bare grid floor. During the time required for a foraging trip, body temperature fell less than 0.5°C, although the skin temperature did drop from about 25° to 10°C.

This example is not trivial. It highlights the way in which, with a sufficient diversity and plasticity in effector mechanisms, it is possible to satisfy different motivations simultaneously. Diversity of effectors has been thought to be of value mainly in providing redundancy should one mechanism be impaired. Richter (1943) showed that behavioral responses often came to the rescue when physiological effectors were damaged. The adrenalectomized rat saves itself by drinking saline solution; the rat with deficient metabolism keeps itself warm by building an extra large nest. However, it is not true that behavior is only a second line of defense for occasions when physiological mechanisms fail.

Sometimes behavior is used right from the start in intact animals. For example, when little effort is required, squirrel monkeys (*Saimiri sciureus*) prefer to thermoregulate by pulling a chain that alters the ambient temperature. When counterweights are added to the device, making the chain hard to pull, then the monkeys rely more on autonomic responses; shivering and increased metabolism substitute for the behavioral response (Adair and Wright, 1976). There can, however, be little doubt that variety in defense has a back-up function.

Variety in defense is also valuable in other ways, as in enabling the appropriate type of defense to be mounted. The response to a hit-and-run attack may be unsuitable for withstanding a siege. For example, baroreceptor reflexes can restore arterial blood pressure in a matter of seconds. Baroreceptors, like other stretch receptors, adapt to prolonged stimulation. Chronic challenges to the maintenance of blood pressure are met in other ways, such as by activation of the renin–angiotensin system or adjusting the blood volume through altered renal excretion. When the sinoaortic baroreceptors are removed from dogs, their mean arterial pressure remains close to normal but the variability is much increased; the loss of the rapid neurally mediated defenses results in much greater changes in response to such minor disturbances as a person entering the room (Cowley et al., 1973).

In addition, multiplicity of defense mechanisms increases the scope for warding off potential conflicts by permitting switching among the array of available effectors (cf. Simon, 1986). Switching between effectors within a homeostatic system is known to occur in defense of a regulated variable when the cost of making particular responses changes. For instance, in a rat thermoregulating in a warm environment, saliva excretion and evaporative cooling increase when bar pressing to obtain cooling is made less rewarding. It seems plausible that the same switching mechanisms could be sensitive to the demands of other nonthermal homeostatic systems (Schmidt, 1984).

It is not always necessary to switch completely from one effector to another to ameliorate conflicts. Sometimes much can be done simply by altering the precise way in which a particular effector is used. For instance, in heat-stressed birds, breathing patterns change in ways that minimize conflicts between acid-base regulation and thermoregulation. Lacking sweat glands, birds depend greatly on panting for cooling, though at least some species also have mechanisms for cutaneous water evaporation (Arad et al., 1987). Respiratory rates in heat-stressed birds can increase by as much as twentyfold (Johansen and Bech, 1984). This would bring about large reductions on $P_{CO_2}$ were it not for the fact that the tidal volume of each breath is less during panting respiration, so that it is largely air to and from the dead tracheal space that is circulated in and out of the body, rather than air from the gas-exchanging surfaces of the lungs. There are various different adjustments of normal breathing that help satisfy the demands of both thermoregulation and chemoregulation. This can be done by simple panting, or by yet shallower panting with occasional flush-out breaths for gas exchange, or by compound respiration (Fig. 2–1).

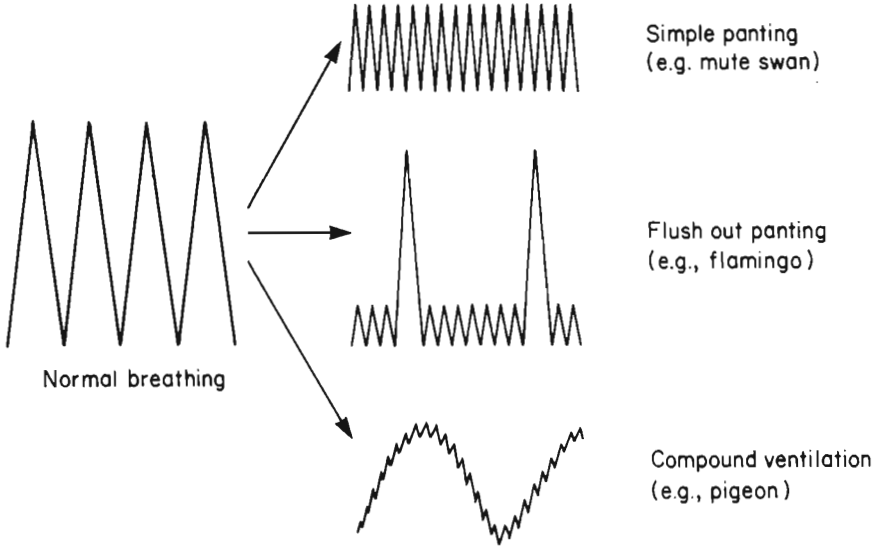



**Figure 2–1.** Diagrams of some different breathing patterns of birds exposed to high ambient temperatures. [From Johansen and Bech, 1984, Breathing and thermoregulation in birds. In *Thermal Physiology,* J. R. S. Hales (ed.), Raven Press, N.Y., p. 342.]

## AVOIDING THE CONFLICT SITUATION

During intense physical activity, to function effectively the muscles require a high blood flow. The skin also requires a high blood flow to dissipate the heat produced. A conflict arises over cardiac output (Stitt, 1979). What happens is that the body becomes warmer, but at a certain point thermoregulatory needs dominate and exhaustion and collapse occur. The ensuing decrease in activity takes the animal out of the conflict situation.

The acceptability of taking this route—avoidance of the conflict situation rather than resolution of the conflict within the situation—is limited by the survival value of remaining in the conflict situation. A man may have to exert himself prodigiously to escape from a pursuing lion. The survival value of continuing to run, even though this puts muscles and skin into conflict over blood supply, may be very considerable. Often conflicts are inherent in living in particular habitats (e.g., the camel in the desert).

## UNAVOIDABLE CONFLICTS IN THE LABORATORY AND FIELD

It may not be possible always to avoid the conflict situation or to resolve the conflict by switching effectors or modifying their action. Despite changes in breathing patterns, respiratory alkalosis does sometimes occur in heat-stressed birds (e.g., Calder and Schmidt-Nielsen, 1966). No regulatory system has an infinitely varied arsenal of defenses. In their experiments with a warm home and a cold restaurant, Johnson and Cabanac (1982b) were able to alter their

experimental situation in a way that prevented the rat from avoiding conflict by switching effectors. They simply increased the distance between the home and the restaurant to 16 m. When this was done, core temperatures of the animals were estimated to be about 1°C lower than when only short foraging trips were required; skin temperatures fell to near 0°C. Food intake also decreased by a few grams, but different testing conditions were introduced before it became clear whether this would have led to declines in body weight. As the distance between the home and the restaurant increased, rather than numerous quick meals, the rats took fewer and longer meals, despite the resultant hypothermia.

Similar experiments have been tried with growing tegu lizards, *Tupinambis teguixin* (Cabanac, 1985a). By using an animal that can maintain its body temperature only by making use of external heat, it is easy to make foraging excursions thermally challenging simply by placing food in a cold area, in this case at 0°C; another unprovisioned part of the test chamber contained a heat lamp. When lizards of this species were satiated, they left the area under the heat lamp when they warmed up to 37°C and returned when they cooled off to about 34°C. This shuttling to and from a heat source is part of normal thermoregulatory behavior. When the lizards had not been fed for a day, they stayed away from the heat lamp for longer periods, until their temperatures fell to around 32°C. Like the rats, when hungry they accepted a small reduction in body temperature. Attempts to accentuate this phenomenon by depriving the lizards of food for longer times were unsuccessful because the lizards did not increase their intake systematically as a function of deprivation duration, but instead grew at slower rates.

Unavoidable conflicts have been especially successfully studied in the pigeon, *Columba livia*. Rautenberg et al. (1980) placed birds in a warm air stream of 50°C or more. The birds could switch on cool 18°C air by pecking at a key. This behavior was necessary because evaporative cooling through panting was operating at maximal rates. With both the panting and the key-pecking behavior, body temperatures stabilized at about 42°C. In the next part of the experiment the pigeons were food-deprived enough to reduce their weights to 80%. They were then able to obtain food in the warm air chamber by pecking at another key. When given access to this second key, they initially neglected the cool air key and allowed their body temperature to rise to 43°C. Similar high temperatures were tolerated when dehydrated pigeons were offered the choice between working for water or for cool air.

So, with persistence, it is possible to study what happens when unavoidable conflicts are arranged. But how instructive are the results of such experiments? It may be asked whether such conflicts would ever arise outside the laboratory. Pigeons can normally fly away from excessively hot places. With the rats in the restaurant experiments, restriction on take-out orders is unnatural. Hoarding is a common behavior in rodents; in male rats it increases when body weight falls (Fantino and Cabanac, 1980). In being offered only powdered food, the animals were prevented from calling up one of their normal body weight defense mechanisms. Similar complaints could be raised about the lizard experiments. The animals used came from the Guianas, where ambient

temperature seldom falls below 20°C. Food at 0°C is something this population of lizards would never be faced with in its own habitat. Generalizing, it might be argued that if artificial conditions were eschewed, then animals could always avoid conflicts by switching between available effectors. A sufficient effector repertoire may have evolved for the niche to which a species is adapted but not for contrived laboratory situations.

There may be some cogency in this argument for particular cases. Nevertheless, there are examples in which clashes between regulatory systems do occur in natural circumstances. The camel's dilemma as to whether to use water to keep cool or to maintain fluid balance has already been mentioned (Chapter 1). Various incompatibilities between feeding and parental care are described in Chapter 4. It is not hard to imagine that an animal, after enduring adverse weather conditions or recovering from sickness, could be both hungry and thirsty at once—and possibly cold as well—with its different regulatory systems simultaneously crying for satisfaction.

A different but naturally occurring conflict is that between courtship of newts, which takes place at the bottom of a pond, and the regulation of blood gases, which requires surfacing to breathe (Halliday and Sweatman, 1976). A similar situation arises with the newborn hippopotamus. Its habit of suckling underwater (Verheyen, 1954) presumably entails some interaction between drives to feed and to breathe, although this has not been studied systematically. In such circumstances the conflict is over control of the behavior of the whole animal. In other cases conflict arises over the control of a particular effector. For example, vasoconstriction in the cold promotes thermal constancy but makes it harder to keep blood pressure constant (Wasserstrum and Herd, 1977b; Wilson and Fyda, 1985).

Even when laboratory environments impose unnatural constraints, they can still be instructive about the mechanisms of interaction between different regulatory systems. Here we come to a more serious limitation of experiments on this subject. They are a valuable starting point, but they do not go much beyond telling us that, in a particular situation, stability of one variable is not strictly maintained. No general rules are provided, no insights are offered into what determines when a particular system wins. What would have happened in the restaurant experiments if the rats had been made hungrier? What would have happened if the lizards had been forced to wait in a cool place long enough to make their temperatures fall below 32°C before they received any food? Perhaps after parametric work with a wide range of hunger and thermal discomfort, it might be possible to predict what an animal would do in particular circumstances.

Another approach is to think about evolutionary fitness. In terms of the contribution to future generations, the benefits minus the costs of the choice made should exceed those of the rejected courses of action. This approach encounters the theoretical problem that an animal might not, in fact, always make the optimal choice, and the practical problem of finding a common currency in which to compare the results of different actions. How does one actually compare the value of foraging with the risks of predation? Dynamic programming may offer some hope of progress on the common currency problem (McNamara and Houston, 1986).

A very different proposal is that, in a multidimensional space of different motivations, animals and people make choices that maximize sensory pleasure (Cabanac, 1985b). For instance, subjects in a cold room can keep warm by exercising, but this makes them tired. Different levels of exercise on a treadmill and of ambient temperature are imposed on the subjects, and their pleasure ratings for each combination are recorded. In other tests they are free to select either the treadmill slope or the ambient temperature. The choices they make correspond roughly to combinations that give maximal pleasure. This level of analysis concerns immediate proximate mechanisms governing the choice, and is not incompatible with analysis in terms of adaptive advantage and fitness.

Despite these interesting suggestions, the matter of finding valid rules of how animals actually behave in conflict situations is in a rudimentary state. At this stage it may, however, be worthwhile to consider some of the general ways in which conflicts could be allowed to proceed.

## STRICT HIERARCHY

There could be a strict and unalterable hierarchy, with one system always taking precedence no matter what. This would surely be maladaptive. Suppose, for example, that water balance were top in the hierarchy, then a starving animal that had only a modest water deficit would look for water rather than food. On teleological grounds, strict hierarchy will not be considered further.

## CONTINUOUS CONFLICT: INHIBITION AND DISINHIBITION

If there is no strict hierarchy, with one system always in the ascendancy, then the animal must alternate between trying to satisfy the demands first of one and then of another system. What determines when such shifts occur? To say that transitions from one behavior to another take place when the level of causal factors for one behavior come to exceed those for the other is a description that may help define the problem, but it is not explanatory. Thought has been given, however, to the ways in which the levels of causal factors for different behaviors can change relative to one another. McFarland (1969) distinguishes two basic changes. Inhibition occurs when the strength of causal factors for one behavior come to exceed those of another and so oust it from control of a final common behavioral pathway. Disinhibition occurs when the strength of causal factors for one behavior falls below that for another and so allows it to gain control. If there are successive disinhibitions, as shown in Figure 2–2d, this is called *chaining* (Cohen and McFarland, 1979). If there are successive inhibitions, this is called *competition* (Fig. 2–2c). This is perhaps an unfortunate term in that, in a general sense, in all cases shown in Figure 2–2 there is competition. Causal factors for both behaviors are always present but can only activate the behavior when they come to exceed the causal factors for other behavior. It is only the ways in which the causal factors change relative to one another that are different. In this book, the term *competition*, or *contin-*

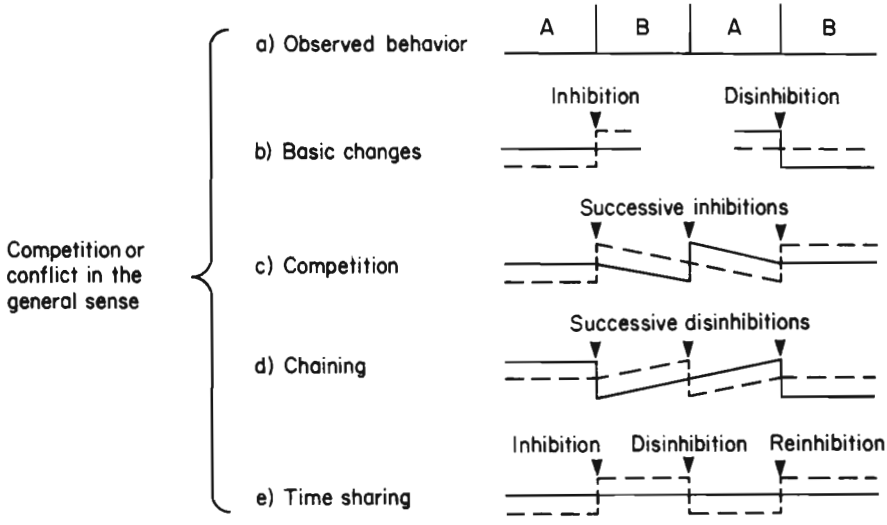



**Figure 2–2.** Some different possible explanations for the alternation between two behaviors, A and B, based on changes in the level of causal factors for the two behaviors. Solid lines show level of causal factors for behavior A; dotted lines show level for behavior B (adapted from Cohen and McFarland, 1979).

*uous competition,* is used in the more general sense, that is for situations in which causal factors for both behaviors are present and attempting to gain mastery, and not just for the specific case of successive inhibitions. The term *continuous conflict* is used in the same general sense.

## TIME SHARING

Another way in which causal factors change relative to one another is by successive inhibitions and disinhibitions (Fig. 2–2e). This is called *time sharing* (McFarland, 1974). In time sharing there is a dominant and a subdominant activity, or, to use computer terminology, a foreground activity and a background activity. The subdominant activity occurs only when the strength of the causal factors for the dominant activity falls below its elicitation threshold. At that time the subdominant activity is permitted to occur. For example, suppose that an animal were both thirsty and hungry, and suppose that drinking were dominant. If the animal were given both food and water, it would first drink for a while. Then for some reason, perhaps the stomach becoming full of water, the causal factors stimulating drinking would decline, and the animal would pause. At that time the subdominant activity of eating would be allowed to occur. Eating would not occur earlier or later if the animal were more or less hungry because the strength of the causal factors acting on the subdominant activity do not influence when it occurs. After a while, perhaps because of water leaving the stomach, the causal factors stimulating drinking would strengthen again, and eating would be cut off.

Time sharing is different from strict hierarchy because it is accepted that there may be reversals between activities occupying dominant and subdominant roles (Cohen and McFarland, 1979). In a slightly thirsty but very hungry animal, eating might be dominant and occur first when the animal is offered food and water, whereas in a slightly hungry but very thirsty animal, drinking might be dominant and occur first. Time sharing has been proposed as an organizing principle operating over fairly short time spans when an animal alternates between two behaviors. In strict hierarchy no switching of behavior occurs until one system is completely satisfied, with a zero level of causal factors.

The essential idea in time sharing is that over the time span when one activity is dominant the strength of the causal factors operating on the subdominant activity has no effect on its occurrence. This is an operational definition. Whether it is met can be discovered by manipulating the causal factors for the behavior that is thought to be subdominant. It says nothing about the possibly different mechanisms that might underlie behavioral sequences meeting the operational definition.

There is some debate about what kinds of data constitute evidence for the existence of time sharing (Houston, 1982; McFarland, 1983). This applies in particular to interruption experiments. Suppose alternations between behaviors are organized as in Figure 2–2e. Then if the dominant activity is interrupted it should be resumed when the interruption ends. If the subdominant activity is interrupted, and if the interruption is short, then that activity should be resumed, but if the interruption is long, then the dominant activity should be resumed when the interruption ends. Various experiments by McFarland and his colleagues demonstrate such asymmetries between interruptions of different activities. For example, when male sticklebacks, *Gasterosteus aculeatus,* are housed in a tank containing a nest at one end and a female stickleback at the other end, they alternate between courting the female and swimming to the other end of the tank to maintain the nest in good repair. Suppose on a given day courting is the dominant behavior. Then if the male is trapped in the middle of the tank while on its way to court the female, when released it proceeds on toward the female. If it is trapped while on its way to tend the nest, it proceeds to the nest if the interruption is short but it returns to court the female after a long interruption (Cohen and McFarland, 1979).

Such data are consistent with time sharing, but they are not sufficient to meet the operational definition of time sharing. Houston (1982) has pointed out that it would be possible to generate similar data by competition between the causal factors responsible for the two activities, if one permits the levels of these factors to change during the interruptions. There may be positive feedbacks and delays in negative feedbacks. Depending on the time courses and interactions of such factors, the initial behavior sequences and how they are affected by interruptions could be determined by the level of the causal factors for *both* behaviors, rather than for just one (Houston and Sumida, 1985). Therefore interruption experiments are not an infallible test of time sharing, as McFarland (1985) has conceded.

Houston's (1982) criticisms weaken the evidence for time sharing mecha-

nisms, but they provide no evidence against their existence. Where there is asymmetry in the results from interruption experiments, and where there are additional data of other types, then time sharing remains a plausible explanation for the organization of the behavior. For instance, in experiments where a hungry rat also has the opportunity to mate, the causal factors for the subdominant activity have been directly manipulated. Sexual behavior in the male rat consists of a series of ejaculations separated by intervals. Brown and McFarland (1979) found that neither the frequency nor the patterning of sexual behavior was altered by increasing the duration of food deprivation from 0 to 48 hours. The rats fitted in eating between ejaculations. Thus manipulation of the causal factors for eating (i.e., increasing deprivation), did not affect when these intervals for eating became available. This suggests that the behaviors were organized on a time sharing basis, with eating as the subdominant activity. However, while time sharing may have been operating once the sexual behavior had begun, something else was occurring at the start of the tests because the hungrier rats took longer before their first interaction with the female; they were busier eating at the time. So by the time they began mating they had already taken the edge off their appetite. It is possible that more than enough time was available during the subsequent inter-ejaculatory intervals to satisfy the remaining hunger, even after 48 hours of food deprivation. It would have been interesting to see whether the patterning of sexual behavior would have been altered had food been offered only after sexual interactions had started.

Whether it turns out that time sharing is widespread, occurs in just a few circumstances, or is not to be found, the idea is an important contribution and has stimulated analysis of possible ways of organizing behavior in situations in which an animal alternates between the demands of two motivations.

## LOWERING REGULATED LEVELS

A competition may be won by overpowering one's opponents. Another way of resolving a conflict is to persuade the other parties that they do not really want the disputed item. Lowering the regulated level of one variable, when conflicts arise, is somewhat akin to the persuasion method. It is a wise way to proceed. Attention is not diverted by the continuing struggle of one of the motivational systems for mastery; causal factors for the behaviors it controls fall to zero. Resources are not wasted in mounting costly defenses.

Yet, it may be objected, it is all very well to extol the wisdom of persuasion, to hint at its esthetic or even moral appeal, but if stability is as necessary as we have been led to think, then how can the body afford to lower the defended level of a variable without incurring damage? Here we come to one of Cannon's most neglected insights, the idea that the normal settings of defended variables are ones that give a margin of safety (1939). This is perhaps Cannon's most important contribution beyond elaborating what Bernard had already outlined. For example, blood sugar is usually kept at 90 mg/dl, but if it rises to 120 mg/dl after a meal, or if it falls to 80 mg/dl, there are no serious consequences; only if it falls to around 60 mg/dl do signs of neurological dysfunction become

evident (Brandes, 1977). Similarly, calcium in the blood is regulated at a level well above that at which convulsions appear. Body fat and body temperature also have safety margins, though in the case of temperature this is small on the upside. Systolic blood pressure may drop from 115 to 80 mm Hg without starving the tissues of oxygen. In fact, the blood pressure of healthy animals is by no means constant: mean arterial pressure in dogs kept in an outdoor run typically varies between 75 and 125 mm Hg over 24 hours (Broten et al., 1988). It should be cautioned that chronic deviations from the normally regulated values might be deleterious. This discussion refers to short or medium duration deviations, which are often well tolerated.

Cannon also considered the value of having a pair of organs, but safety deriving from spare capacity in the effector systems is different from that arising from the judicious choice of regulated levels. Overall, Cannon regarded the margin of safety as just that—safety against disaster. He quoted analogies about engineers who, after calculating the stresses that a bridge will have to endure, double or treble the strength of the supports, as a safety factor. Cannon's view of the body's safety margin was similar: its prime function was insurance against collapse. This is certainly appropriate for a physician but there may be more to it than that. Setting regulated levels somewhere between dangerously high and low limits permits flexibility in the defended levels and allows homeostasis to be used in a more creative dynamic manner. In particular, it makes altering of defended levels in conflict situations a viable option.

## CHOICE AND COMBINATION OF REACTIONS TO POTENTIAL CONFLICTS

Three general approaches to conflict have been described. The first is to find some means of achieving one's end that does not involve conflict. The second is to wage battle under some set of rules that decides who is the winner at any particular time. The third is to persuade one's opponent, or oneself, that the item in dispute is not after all wanted that much. These correspond to (1) switching between effector mechanisms, (2) continuous conflict, and (3) alterations of defended levels, or rheostasis.

These three approaches to conflict are not mutually exclusive; they may be used in various combinations. Switching of effectors may go some way towards avoiding conflict, yet still leave a remnant to be decided by the strength of the relevant causal factors. Rheostasis may go some way toward avoiding conflicts, but if, despite lowered levels for defense, the value of the regulated variable falls lower still, then conflict may emerge.

There are circumstances in which one of the three strategies listed above probably would be emphasized. When there are severe limitations to how much the defended level of a variable can be lowered, continuous conflict will probably persist. For example, the male newt courting the female at the bottom of a pond can incur only so much oxygen debt; eventually it must rise to the surface to survive. There may perhaps be some changes in the thresholds of blood gas concentrations required to initiate breathing; with a female newt so

unresponsive to the male that the courtship sequence can never be completed, breaths in the male occur about once every 4 minutes compared to every 3 minutes in a non-sexual situation (Halliday and Sweatman, 1976). Measures of the volume of air taken at each breath and of blood gases are needed to determine if there is indeed a change in the defended levels of blood gases. But the main way that breathing and courtship interact is by a continuing competition. In highly sexed males, breathing occurs less often and is inhibited by the presence of a female. When the female is suddenly removed by the experimenter, breathing is disinhibited (Halliday and Sweatman, 1976). That males come up for air very soon after the female is removed in such tests suggests that strong motivations to breathe were present previously.

Another situation in which continuous conflict predominates is when two behaviors require the same final common behavioral pathways for achieving something relevant to a single motivational system. For instance, in the male stickleback, nest care and courting both require the animal's presence and attention. Nest care is stimulated, not damped down, by the sight of the female fish (Cohen and McFarland, 1979). As both are necessary for successful reproduction, decreasing the output of reproductive hormones would not be adaptive in this situation. Some kind of continuous conflict, with alternation between the two behaviors, seems inevitable. Whether this alternation is arranged by time sharing or by some of the other ways shown in Figure 2–2 is a secondary point. Time sharing is one way of avoiding going back and forth between two activities without ever spending long enough on one to achieve anything useful. However, it is not the only way to avoid dithering. If positive feedbacks are generated at the start of an activity, then dithering can be avoided even if there is competition between the causal factors for the two activities.

When there is an opportunity to anticipate a potential clash and minimize the threat by building up margins of safety in advance, then rheostasis may be preferred over a back-and-forth tug between the causal factors for alternative courses of action. For instance if food gathering is likely to detract from breeding, then fat may be stored in advance, and its regulated level can be turned down later during the reproductive season. Changes in regulated levels may also be appropriate when the dispute is not for a final common behavioral pathway but for a commodity like water, as in the camel when the defended level of temperature changes to avoid the need for using water. It is also tempting to think that a lowering of defended levels may be more common when the potential conflict is prolonged, whereas a continuous struggle may be more common over short time scales. However, it may be unwise at this stage to underestimate the speed with which regulated levels can change.

## SUMMARY

Conflicts between different regulatory systems can often be avoided by selecting between an array of available effector mechanisms in a way that allows the demands of both systems to be satisfied. However, there are both natural and

contrived laboratory circumstances where conflicts cannot be defused in this way. In such situations there are two other not mutually exclusive possibilities:

1. Continuous competition (conflict): the regulatory systems continue to compete for response pathways with the outcomes settled by some as yet undefined rules. Transitions between incompatible behaviors could occur through various sequences of inhibition and disinhibition.
2. Lowering of defended levels in one system: this is an example of rheostasis and is often possible when there is some margin of safety between the level at which a variable is regulated and that at which survival of the organism is jeopardized.

## PREVIEW

Before embarking on a survey of examples of rheostasis, there is a pause in the next chapter for clarifying terminology.

# 3

# Terminology and Definitions

## RHEOSTASIS OR HOMEORHEUSIS?

In this book the term *rheostasis* is used to describe regulation around shifting set-points. In 1977 Nicolaïdis, recognizing that such phenomena were widespread and needed designating, constructed the word *homeorheusis*. The *stasis* in Cannon's homeostasis was replaced with *rheusis* to convey something flowing rather than static. However, Cannon (1929) did not use *stasis* to imply something static but to convey the idea of a condition or general state. He was explicit about this.

> Objection might be offered to the use of the term *stasis*, as implying something set and immobile, a stagnation. Stasis means, however, not only that, but also a condition; it is in this sense that the term is employed. *Homeo*, the abbreviated form of *homoio*, is prefixed instead of *homo*, because the former indicates "like" or "similar" and admits some variation, whereas the latter, meaning the "same," indicates a fixed and rigid constancy. As in the branch of mechanics called "statics," the central concept is that of a steady state produced by the action of forces; *homeostatics* might therefore be regarded as preferable to homeostasis. The factors which operate in the body to maintain uniformity are often so peculiarly physiological that any hint of immediate explanation in terms or relatively simple mechanics seems misleading. For these various reasons the term homeostasis was selected.
>
> (Cannon, 1929)

Whether or not Cannon's use of Greek words was too liberal is debatable. The fact is, the term *homeostasis* has become part of the English scientific vocabulary. I therefore prefer to replace the *homeo* with *rheo* to describe a condition that is regulated at changing rather than similar levels or values, and to accept Cannon's point that the condition is a product of dynamic processes, rather than being something that remains the same merely through stagnation. Another advantage of the term *rheostasis* is that it triggers association with the

word *rheostat;* a rheostat precisely and vividly exemplifies a device whose setting may easily be adjusted.

A further reason for not taking up Nicolaïdis' (1977) use of the term *homeorheusis* is that 20 years earlier Waddington (1957) employed "homeorhesis" as an alternative to "canalization." Waddington's terminology, such as "homeorhetic cross-section" in the "epigenetic landscape," is related to a particular way of visualizing some of the features of development. Moreover, the term is limited to development; it refers to the tendency to return after perturbation to specified paths or developmental trajectories rather than to fixed states. As such, it is not broad enough to cover the full range of circumstances in which alterations in regulated levels occur—e.g., temporary alterations in response to pathogens.

## RHEOSTASIS

*Rheostasis* refers to a condition or state in which, at any one instant, homeostatic defenses are still present but over a span of time there is a change in the regulated level. Therefore rheostasis includes a change in set-point, both when the term is used descriptively without specifying a mechanism (Chapter 1) and when it is used to indicate a mechanism comprising negative feedback with a reference signal.

Change of a variable that is normally defended is not in itself proof of rheostasis. When changes take place with great regularity or repeatability, they may constitute highly circumstantial evidence for rheostasis, just as stability constitutes highly circumstantial evidence for regulation around a constant level. Stronger evidence for rheostasis is a demonstration of defense of different values of a variable at different times or in different circumstances.

## SLOW AND SUDDEN CHANGES

Rheostasis may apply to both gradual and sudden changes. Whether something is rapid or gradual depends on the frame of reference, and whether something changes in a continuous manner or in one step depends on the resolving power of experimental methods; something that appears continuous may in fact be composed of rapid discrete steps. If set-points remain the same for only short periods, it may be difficult to study responses to challenges before set-points have altered.

Terms like *sliding set-point* or *climbing set-point* are not informative about the precise mechanisms of change. They may, nevertheless, be used to describe cases in which changes continue for a time long enough for it to be feasible to test whether different set-points are operative at different stages in the adjustment process. It is possible that, during cycles, set-points may change continuously and that stable values are never reached. Rheostasis does not imply that new stable levels are reached, only that there is a change in regulated levels.

## PROGRAMMED AND REACTIVE RHEOSTASIS

Two circumstances in which rheostasis occurs can be distinguished. Changes in defended levels may be obligatory at certain phases of the life cycle and may occur regardless of conditions. These will be referred to as examples of programmed rheostasis. *Programmed rheostasis* is often cyclical, though it need not be so. There may also be developmental, once-in-a-lifetime examples of rheostasis. *Reactive rheostasis* occurs in response to stimuli, stimuli that may or may not be encountered.

This distinction between programmed and reactive rheostasis, as that between slow and sudden changes, is not always clear cut. Rheostasis during pregnancy and lactation may be considered to be part of the reproductive program, once pregnancy is initiated, but it also may be considered reactive in that pregnancy is not inevitable. In this book rheostasis in association with reproduction will be included in the programmed category because reproduction is a common part of life cycles. Really there is a continuum between programmed and reactive rheostasis, with interactions between the two being possible. It is still useful to distinguish the ends of a continuum. The temperature changes in camels again provide an instructive example (Fig. 1–5). The daily warming is programmed in that it happens whether the animal has access to water or not. But the extent of the temperature rise is greater if the camel lacks water. This part of the change is reactive because it depends on the immediate situation. It is something separable that occurs in addition to the obligatory change. The reactive and the programmed changes work together in this case; they are not mutually exclusive.

## OTHER REJECTED TERMINOLOGY: PREDICTIVE HOMEOSTASIS

Moore-Ede introduced the term *predictive homeostasis* (1986) for "corrective responses initiated in anticipation of a predictably timed challenge." Used in this way only, predictive homeostasis is equivalent to anticipation or feedforward, which others have recognized as an important part of homeostatic mechanisms (Chapter 1). In fact, Moore-Ede applies his term to various different aspects of homeostasis and rhythmic processes. In places, rhythmic changes in set-points are included as examples of predictive homeostasis. Mostly, however, Moore-Ede talks about "predictive homeostatic responses." For example in man, the response to infusions of potassium ($K^+$) varies according to the time of day, urinary excretion of $K^+$ being much less at night. These are called *predictive circadian modulations,* in that usually at night people eat little and so there is little need to excrete excess electrolyte. The poorer excretory response at this phase of the cycle needs to be distinguished from any changes in regulated levels of $K^+$. Another example relates to an animal pressing a lever in anticipation of receiving food: this is also called *predictive*. When the animal presses the lever to obtain food that is actually available, this is called *reactive*. There is no implication that set-points are different; in both cases the bar pressing corrects or attempts to correct energy deficits.

Even when predictive homeostasis is applied to a set-point change, it is not always transparent that Moore-Ede's definition is met. For instance it is not obvious that a lower body temperature set-point in man during the early hours of the morning is a corrective response initiated in anticipation of a predictably timed challenge. It might just as plausibly be perceived as a way of avoiding having to make corrective responses at that time. Similarly, the higher regulated temperatures of rats during the night might be seen as a way of reducing the need to initiate heat loss responses.

These various points show that the term *predictive homeostasis* is being used too loosely and generally to be helpful in the present discussion. The term *rheostasis* is retained as applying specifically to changes in regulated levels. Whether or not effector systems also change is an interesting but separable question. *Programmed rheostasis* covers circadian changes but also encompasses changes in set-points occurring during ontogeny. *Reactive rheostasis* is clearly different from Moore-Ede's reactive homeostasis. The latter is simply part of usual homeostasis and carries no implication of a change in defended levels, whereas such a change is the essence of reactive rheostasis.

Nevertheless, one may agree with Moore-Ede (1986) that the relationship between homeostasis, biological rhythmicity, and predictability is fundamental. It can profitably be reconsidered and illustrated with contemporary examples (Moore-Ede, 1986). As Aschoff (1964) put it:

> Homeostasis is a shielding against the environment, one might say, a turning away from it. For a long time, this phenomenon has been taken as the prime objective for an overall organization in physiology; and it evidently has great survival value. But there is another general possibility in coping with the varying situations in the environment: it is, instead of shielding, "to turn toward it"; instead of keeping the "milieu interne" stable, to establish a mirror of the changing outside world in the internal organization. This has one clear prerequisite: the events in the environment must be predictable, which, of course, is the case when they change periodically.

The essential additional point that rhythmic changes do not involve a contradiction of homeostasis was cogently put long ago by Halberg (1953; see also Aschoff, 1970; and Mrosovsky, 1976, for further discussion):

> The conception suggested here resembles Cannon's principle of homeostasis with the important difference that the base-line about which variations are held to occur is not the straight line (and its range of "common variation") which has been postulated since Claude Bernard developed the concept of the constancy of our internal environment. The "base-line" is rather the *curve* of a 24-hour cycle . . . data are interpreted as variations from a 24-hour curve rather than from an assumed horizontal line.

## SUMMARY

1. *Rheostasis* is defined as a condition in which, at any one instant, homeostatic defenses are present but over a span of time, there is a change in the level that is defended.

2. The term *rheostasis* is preferred over the term *homeorheusis* as being more in accord with Cannon's use of the word *stasis* and his recognition that steady states are a product of dynamic processes.
3. Rheostasis implies change in regulated level, whereas the phrase *predictive homeostasis* has also been applied to changes in effector systems and is therefore insufficiently precise.
4. *Programmed rheostasis* refers to changes that are obligatory at certain phases of the life cycle. *Reactive rheostasis* occurs in response to stimuli that may or may not be encountered. It is emphasized that the distinction between programmed and reactive rheostasis is not always clear cut. These subcategories are used partly as a matter of convenience and to indicate the range of circumstances in which rheostasis occurs.

## PREVIEW

It would be pointless to fuss over definitions if rheostasis were not common and biologically important. The next three chapters provide numerous examples and candidate examples of rheostasis.

# 4

# Programmed Rheostasis

A safety margin in the regulated level is necessary if rheostasis is to occur without untoward consequences (Chapter 2). Safety itself—nutritional and energetic safety—is a major function of depot fat. This makes body fat regulation a prime candidate for exhibiting rheostasis. If defenses for maintaining fat were rigid, perfect, and powerful, then it could not serve its function as a reserve (Keesey and Powley, 1986). Seasonal changes in food availability, and in breeding activities that compete with foraging, make reserves particularly important at certain times in the life cycle. It is not surprising therefore to find that there are some excellent examples of programmed rheostasis for body fat.

## INCUBATION ANOREXIA

In chickens, ducks, geese, pheasants, and various other birds incubation falls entirely to one partner. With a single bird responsible for the clutch, a potential conflict arises between keeping the eggs warm and protected and searching for food (see also Harvey, 1971). Attentiveness to the nest usually wins, with the result that there is a considerable weight loss over the course of incubation. For example, domestic chickens and junglefowl (*Gallus gallus spadiceus*) lose 10–15% of their weight in the course of incubation (Hellwald, 1931; Sherry et al., 1980). The birds are anorexic rather than aphagic, but intake is insufficient to maintain weight.

Such weight losses were formerly attributed to the "rigors of nesting" (Folk et al., 1966) and the energetic "drain of incubation" (Breitenbach and Meyer, 1959). Various experiments with junglefowl suggest that this view is incorrect. If food is placed within reach of the incubating hen as she sits on her eggs, she still eats little and loses weight. Anorexia amidst plenty strongly suggests that set-points are lowered. How else does the incubating bird resist eating more of the food right under her beak while her weight falls by 10%? In nonincubating chickens a 10% weight loss is enough not only to make them eat but also to work to obtain food (Collier, 1969).

Suspicions that regulated levels are lowered during incubation are confirmed by depriving junglefowl hens of food altogether for a 6-day period. When food is returned, they eat more than usual, and their body weights rise to levels that might have been expected at this stage of incubation in unmanipulated birds (Fig. 4–1; Sherry et al., 1980). This shows that there is no proximate constraint on eating plenty. Deprivation–refeeding experiments give similar results both early and late in incubation, showing that there is a sliding set-point for weight.

Data on the incubating behavior confirm that the progressively lower and lower body weights are still defended. If deprivation is continued too long, then the hen abandons the nest altogether. Even after the first two or three days of deprivation, she leaves the eggs more often and remains away longer during each bout of nest inattentiveness. These lengthening absences probably reflect searching for food; the food hopper in the deprivation experiments was not within reach of the nest. During the day after food is returned, the total amount of time off the nest reaches its highest value. Presumably much of this time is spent in feeding and related activities; certainly the birds' intakes are highest on this day (Fig. 4–1).

Decreased nest attentiveness or desertion of the nest shows that the extent of body weight rheostasis has been limited. It cannot resolve all conflicts. In Chapter 2, rheostasis was distinguished from continuous competition as a way

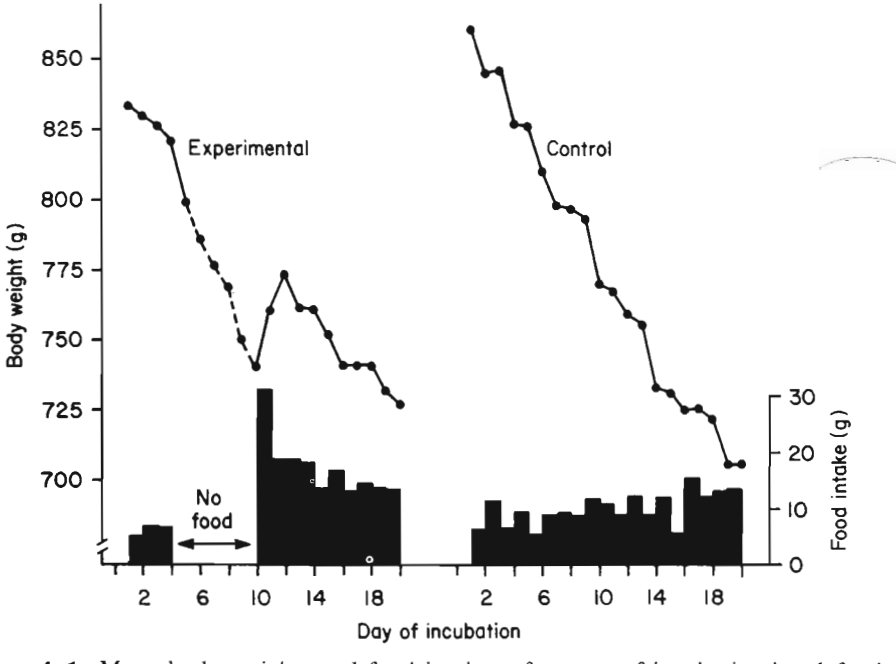



**Figure 4–1.** Mean body weights and food intakes of groups of incubating junglefowl. Dotted line shows weight on days when the experimental group was deprived of food. (Adapted from Mrosovsky and Sherry, 1980, *Science* **207**, p. 839. © 1980 AAAS.)

of resolving conflicts. But if, even despite a lowering of the set-point for a variable, the actual value falls to a yet lower value, then conflict re-emerges. This permits reasonable decisions to evolve. In the present example, a time when there is no food to be found and the hen is becoming thin is hardly auspicious for raising a brood; better to abandon the nest and try again another year. In species breeding in places where food is extremely scarce and the weather harsh, the threshold value for the decision to leave the eggs becomes critical. Snow geese, *Chen caerulescens,* nest in the Arctic; even a successfully breeding female that arrives on the nesting grounds in good condition has barely enough reserves to see her through incubation. Nests are built in drier areas. To feed, the geese have to travel to lower, thawed ground where they can dig for roots, though during late incubation some vegetation may become available nearby (Ankney, 1977). If the animals are to breed at all in such conditions, then the decision to abandon the nest cannot be made too readily. Nest attentiveness is so well developed that some birds starve to death on the nest (Harvey, 1971; Ankney and MacInnes, 1978).

Body weight rheostasis during incubation in the junglefowl is clear cut. It presumably occurs in other single-sex incubators. There are extensive data on body composition of waterfowl (e.g., Ankney and MacInnes, 1978; Krapu, 1981). Fat depots are much reduced, but other tissues also contribute to weight loss, for instance breast muscle, gizzard, and reproductive tract. Nevertheless appetite is reduced. Recent observations on Canada geese, *Branta canadensis maxima,* are instructive. Usually Canada geese arrive at their breeding areas in the far north when snow is still on the ground. There is also a population nesting further south, in Toronto, on islands where fresh grass is available in abundance during incubation; the birds take some of this, but not enough to prevent them losing 20% of their weight over incubation (Mainguy and Thomas, 1985). This is a natural version of the near-food condition in the experiments with junglefowl, and it seems likely that the underlying mechanisms are similar.

Programmed weight loss during incubation may have evolved as a way to permit the mother to stay on her eggs, keeping them warm and guarding them from predators. This would explain the anorexia of geese nesting in Toronto, where food for them is relatively abundant. There may be other or additional adaptive advantages. For instance, the golden pheasant, *Chrysolophus pictus,* hardly ever leaves her nest during incubation. Grasses that are normally eaten are allowed to grow up around the nest. This is also a natural version of the experiment with food pots placed within reach of incubating junglefowl. For the golden pheasant the benefit of anorexia might be that it permits nearby camouflage to remain intact (Goodwin, 1948).

Another possible advantage of incubation anorexia is that it leaves the bird lighter when it comes to providing for its offspring. This may be especially important for altricial species. For instance, Freed (1981) has calculated that each day the house wren, *Troglodytes aedon,* takes off and lands 1,200 times, flies 15,000 m, and walks another 3,000 m to obtain food for the nestlings. Weight loss should contribute to the efficiency of this "flying machine." The female house wren loses just over 8% of her weight during incubation and an-

other 4% when caring for the young, even though the male shares in the latter activity. The benefits of jettisoning weight have been considered also by Norberg (1981), who calculated that if the energy saved went into supplying extra food, it should be enough to increase the survival probability of the young. But if being thinner makes for more efficient foraging, then why put on the extra weight in the first place? Perhaps the answer is that this is a temporary measure needed for times of scarcity or reproductive output. Later, when the young are being fed, food is more plentiful and selection pressure for having fat reserves decreases (Norberg, 1981). Details of food availability, metabolic rates, and life history are needed to make a convincing case for a particular ultimate factor being responsible for weight loss. The more general point, that weight loss in breeding birds may be adaptive rather than induced by stress, is becoming recognized (Mrosovsky and Sherry, 1980; Freed, 1981; Norberg, 1981; King and Murphy, 1985). A lighter flying machine might be one of the reasons, in some species.

## BODY WEIGHT CYCLES IN HIBERNATORS

Most mammalian hibernators have seasonal cycles of body weight. In adult animals, weight changes can be largely accounted for by changes in fat. Deprivation–refeeding experiments show that regulation of weight (more strictly speaking, regulation of fat or some correlate) is present throughout the cycle (Mrosovsky and Fisher, 1970; Heller and Poulson, 1970; Canguilhem and Marx, 1973; Barnes and Mrosovsky, 1974; Fig. 4–2). During the winter phase, even in the caloric abundance of the laboratory, weight is lost. What is the adaptive value of becoming anorexic and losing weight even when food is available *ad libitum*? Why not maintain energy reserves for reproductive activities in the spring, when snow may still be on the ground and food scarce (Mrosovsky, 1971)? Wasting resources in the winter in a fruitless search for food that is predictably absent in the natural environment is part of the answer. But there may be a second reason, especially applicable to hibernators.

To understand this, it is first necessary to consider the phenomenon of periodic arousals from hibernation. Mammalian hibernators do not remain in a torpid state for months on end. Periodically they warm themselves up again for a day or two and then return to hibernation for another bout of a few days to two weeks. One reason for these energetically expensive arousals may be to eliminate metabolic end products from the blood stream. During deep hibernation, renal function, especially glomerular filtration rate, is diminished (Zatzman, 1984). Normal urine production by the kidney is restored when the animals warm up. Thus, periodic arousals contribute to homeostasis by keeping the levels of urea and other metabolic end products within acceptable limits.

Evidence for this hypothesis is reviewed elsewhere (Mrosovsky, 1971; but see Geiser and Kenagy, 1988). Of particular relevance here is that the frequency of arousals (i.e., the need to clear the blood stream of wastes) depends on whether the animal has eaten just prior to becoming torpid. During the middle of the season, when hibernation bouts are longest, virtually nothing is eaten

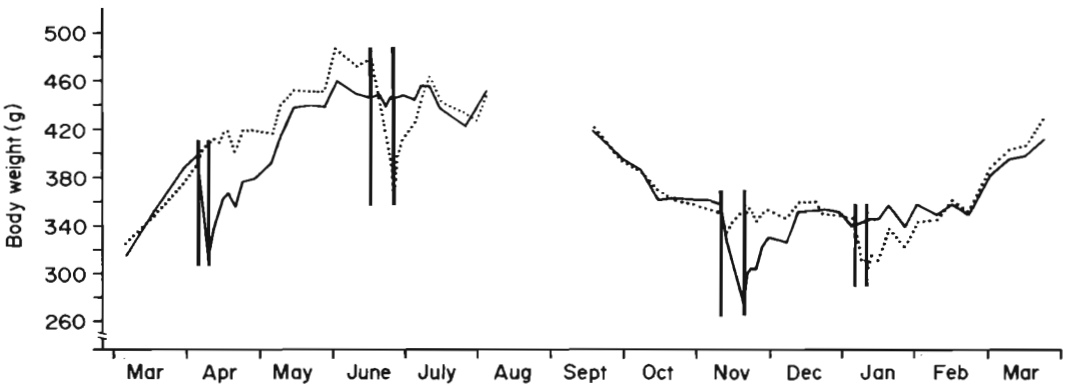



**Figure 4–2.** Seasonal body weight cycles of two groups of European hamsters. During the periods marked by the vertical lines fasts were imposed on one or the other of the two groups. (Adapted from Canguilhem and Marx, 1973, Regulation of the body weight of the European hamster during the annual cycle. *Pflügers Arch.* **338,** p. 172.)

during periodic arousals. At the end of the season, when bouts are shorter, food intake is higher; at these times longer bouts of hibernation can be induced by food deprivation (Mrosovsky and Barnes, 1974).

If one accepts the metabolic end-product account of periodic arousals, it becomes evident that appetite must be switched off over the hibernation season. If it is not switched off, the animal will become motivated to obtain food, either by eating from hoards or by foraging. But eating will reduce the length of hibernation bouts and so vitiate the overall strategy of saving energy by torpor over the winter season. Eating must be reduced, but this leads to weight loss. Falling below the body fat set-point normally promotes a search for food and compensatory eating. To avoid compensatory responses the set-point must be lowered. As a result, even if the animal is provided with abundant food, it loses weight.

An endogenous regulated circannual body weight cycle is a mirror of the environment, reflecting the seasonal alternation between abundance and scarcity. For hibernators, it also reflects the physiological incompatibility between eating and then becoming torpid for long periods. This incompatibility is resolved by the progressive lowering of set-points over the hibernation season. The success of this strategy depends, of course, on there being a prehibernation elevation of set-point and anticipatory fattening.

## PREMIGRATORY FATTENING

Migration is another solution to the problem of winter shortages. Energy is required to sustain the journey, and many species display premigratory fattening. Rheostasis for body fat occurs at such times: after deprivation and refeeding, weights catch up to levels typical for undeprived controls. This effect has been demonstrated in white-crowned sparrows, *Zonotrichia leucophrys,* at several points during both the vernal and the autumnal premigratory weight gains (King, 1963). When the sparrows are catching up after deprivation, their weight gains are steeper than those seen during normal premigratory fattening. This means that normally the animal does not switch into a mode of maximal weight gain but tracks a steadily climbing set-point. That weight gains are not taking place at maximal possible rates is also evident from the greater gains seen in sparrows with ventromedial hypothalamic lesions (Kuenzel and Helms, 1970). Defense of body weight around climbing set-points has also been demonstrated in garden warblers, *Sylvia borin,* by depriving them at various stages in their fall fattening (Berthold, 1975, 1976, 1977).

## WINTER WEIGHT LOSS WITHOUT HIBERNATION

The Svalbard ptarmigan, *Lagopus mutus hyperboreus,* lives in the high Arctic (circa 80°N). It becomes fat in the autumn; having 30% of its weight as fat is quite common. These reserves are lost during the continuous winter night. Not

only is it dark during this time of year, but warm rainy interludes followed by freezing often leave the ground covered with a sheet of ice. Since the Svalbard ptarmigan is herbivorous, this reduces access to food (Mortensen et al., 1983). The weight loss is not a direct result of lack of food because it occurs in captive birds living in outdoor cages provided with food *ad libitum* (Mortensen and Blix, 1985). If food is withheld for 7 days and then returned, there is compensatory eating, and the weight returns to values normal for that time of year (Fig. 4–3; Mortensen and Blix, 1985). Similar tests in the autumn, when the birds are fatter, show that regulation of body weight (>0.9 correlation with body fat) is also present then, but with higher defended levels.

Programmed rheostasis has presumably evolved in this case because it is unlikely that mid-winter foraging will be successful. There is not any obvious conflicting mid-winter activity that would prevent feeding. However, if not migrating is part of this animal's life strategy for exploiting a particular niche unused by other species, then rheostasis in body fat might be viewed as necessary for successful breeding. To make this argument with any conviction, one would need to know more about the natural history of this species. The main thing to note is that, once again, when tests for defense are applied, evidence for sliding set-points is obtained.

Natural experiments can also supply evidence that weight loss over the winter is regulated. The grey plover, *Pluvialis squatarola,* like a number of shorebirds, lays down fat in the autumn and loses it over the winter. When high winds prevent these birds from feeding on mudflats, weight loss is steeper than usual, but there is recovery to usual winter levels when better weather returns.

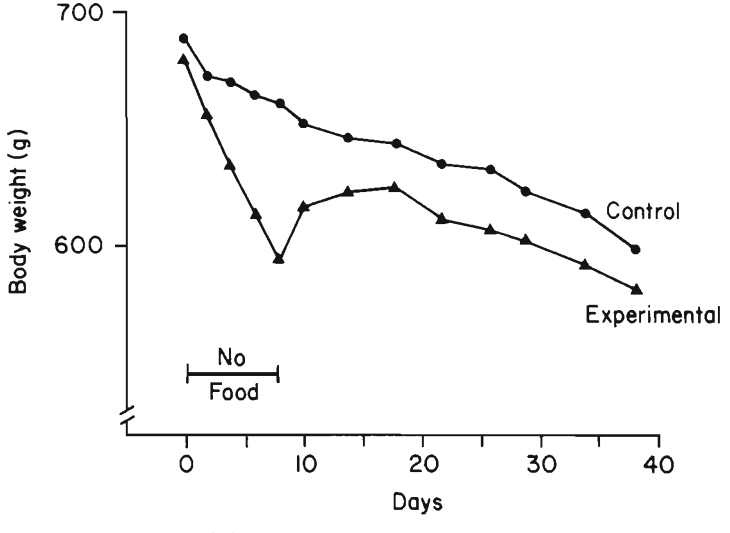



**Figure 4–3.** Body weights of Svalbard ptarmigans. The experimental group was deprived of food for 8 days during December. The control group was fed *ad libitum*. Weight loss is normal for this species at this time of year (adapted from Mortensen and Blix, 1985, *Ornis Scand.* **16,** p. 22).

For grey plovers fattening may be insurance against winter gales rather than against the cold temperatures of this season (Dugan et al., 1981).

## CANDIDATE EXAMPLES OF RHEOSTASIS FOR BODY FAT

Changes in defended weights have been demonstrated during incubation by single parent birds, during weight cycles in mammalian hibernators, during premigratory fattening, and in seasonal weight changes without either migration or hibernation. There are numerous other examples of animals gaining weight at one part of the life cycle only to lose it again at another, but tests of defense have not been made, so strong evidence for rheostasis is lacking. General considerations, however, often make body fat rheostasis a plausible candidate.

When an animal becomes anorexic and loses weight despite the presence of readily available food, a sliding set-point for weight may be suspected. The alternative is to have the animal getting hungrier and hungrier but continuing to lose weight because some competing activity directly inhibits eating. This is implausible when food is accessible and there is no obvious proximate competing activity. For instance, male red deer, *Cervus elephas*, lose ~14–17% of their weight during the rutting season, yet there is grass and other vegetation right underfoot. The females maintain their weights at this time (Mitchell et al., 1976). Blaxter et al. (1974) showed that weight loss occurs in the stags even if they are in captivity, fed *ad libitum* but without the opportunity to perform their full reproductive activities. They suggested that the weight loss was "due as much to an essential inappetance as to the excesses and worries of domestic life." Similar phenomena also occur in other species of deer (French et al., 1960; Wood et al., 1962; see also McMillin et al., 1980). The same types of argument apply to the weight loss of ducks over the winter. Green-winged teal (*Anas creca*) on the high plains of Texas spend only about 5 hours a day feeding. Both time and food are sufficient for them to maintain body energy balance (Baldassarre et al., 1986). Canvasbacks (*Aythya valisineria*), kept indoors in a warm room and fed *ad libitum*, lose weight at similar rates to ducks kept out of doors with plenty of food provided (Perry et al., 1986). This suggests the presence of an endogenous programmed change in reserves.

Sexual differences in weight loss occur in some carnivores as well as in deer. For instance, male polecats, *Mustela putorius*, lose 25–30% of their weight in the late winter. These changes occur in captive animals offered food *ad libitum* (Korhonen and Harri, 1986). Putting this together with the fact that the females in these experiments were able to maintain weight, it is probable that the weight loss in the males is regulated.

Similar considerations apply to beavers, *Castor canadensis*. The adults and young winter together in the lodge. The adults lose weight over the winter, although food is available. Tree trunks are cached in front of the lodge. This food must be easily obtainable because the young beavers actually gain weight over the winter (Novakowski, 1967). Perhaps decreased appetite in the adults is adaptive because it leaves more for the offspring in the event that a freeze-

up occurs before the cache is complete, or in some other crisis. Whatever the evolutionary pressures, rheostasis in body fat is likely to be the mechanism.

The epitome of weight loss in the presence of readily available food is found in mouth-brooding cichlids. These fish lose their appetites during the weeks when they keep eggs or young in their mouths (Fryer and Iles, 1972; Mrowka, 1984), and this provides a way for aquarists to tell if their fish have spawned (Goldstein, 1973). It would be a powerful competing factor indeed that prevented a normally predacious fish from eating a tasty morsel right in its mouth if it were hungry. Presumably it is not hungry when brooding. Although little is known about weight regulation in fish, or about the contribution of the various body compartments besides fat, an obvious way that hunger might be turned off is to lower regulated weight levels.

Numerous other examples of anorexia in the animal kingdom have been reviewed elsewhere (Mrosovsky and Sherry, 1980). Only a few further points will be made here. Food is not always close by when weight losses occur. Bull seals become emaciated while they defend their harems on land (Osgood et al., 1914; Bartholomew, 1953). To find food they would have to enter the water and run the risk that in their absence other males would mate with their females. Even though the case is not so strong as when food is right close at hand, it is still plausible that set-points for fat are lowered during breeding, since in many species weight loss normally motivates a search for food. In people on restricted rations interest in sex diminishes (Keys et al., 1950), and one might expect the same in seals if set-points were not lowered. The fact that the bulls are fat when they haul out of water at the start of the breeding season is also worth noting. Cichlids also gain weight before they breed (W. Mrowka, 1985, personal communication). In general, fattening often precedes anorexia in animals. Reserves are built up before incubation, hibernation, migration, or wintering in cold regions. Anticipatory weight gain followed by weight loss obviously is no more than circumstantial, but given its occurrence in cases in which defense of body weight around sliding set-points has been experimentally demonstrated, it provides an indication that tests for rheostasis might well be positive.

## BODY WEIGHT DURING THE ESTROUS CYCLE

So far this account of programmed rheostasis has concentrated on major seasonal changes in body weight. In many species body weight also rises and falls in synchrony with the estrous cycle. In small rodents, the periodicity of these changes is too short to permit convincing tests for sliding set-points by the usual methods of imposing a period of deprivation and then following weight after refeeding. However, tests of hoarding behavior support the view that the defended weight level changes during the estrous cycle.

The amount of food that rats carry back to their home cages during a test period is proportional to the amount that their body weights have been brought below *ad libitum* levels by food restriction (Fantino and Cabanac, 1980). Hoarding can therefore be viewed as a defense mechanism that is activated by

a discrepancy between actual and defended weight. The body weight at which hoarding falls to zero is taken as the set-point (Fig. 4–4). This value is usually quite close to the body weight of freely feeding rats. There can be a 13% difference in a few individuals between the estimated body set-point and the free-feeding weights, but these are the extreme values. On average, there is not more than 5% (~ 10 g) difference between the projected set-point weight (zero hoarding) and the free-feeding weight (Fantino and Cabanac, 1980). The method is sufficiently reliable to be used for studying set-point changes such as those that occur during the estrous cycle.

Rats and hamsters hoard less at estrus than at diestrus, even when given food *ad libitum* (Herberg et al., 1972; Estep et al., 1978). Hoarding is not reduced to zero in undeprived female rats; some unknown factor maintains a low level of hoarding, even when they are in estrus and presumably not below their set-point (Coling and Herberg, 1982). Nevertheless, deprivation exerts a major influence on the behavior. In female rats, both at estrus and at diestrus, hoarding increases proportionally with body weight loss (Fantino and Brinnel, 1986). At both phases of the cycle the proportionality constants are similar, but at estrus the line relating hoarding to weight intercepts the weight axis at a lower level, indicating a downward shift in the set-point (Fig. 4–4).

Such a shift probably depends directly on high levels of estrogen. This interpretation is reinforced by data from ovariectomized rats. After the operation these rats hoard more until their body weights level off at a higher plateau; hoarding then slackens. Both increased hoarding and weight gain after ovariectomy can be counteracted by injecting estradiol (Coling and Herberg, 1982). Again hoarding and feeding go together; ovariectomy augments feeding, but this slackens as the animals attain higher weights. Estradiol injections decrease

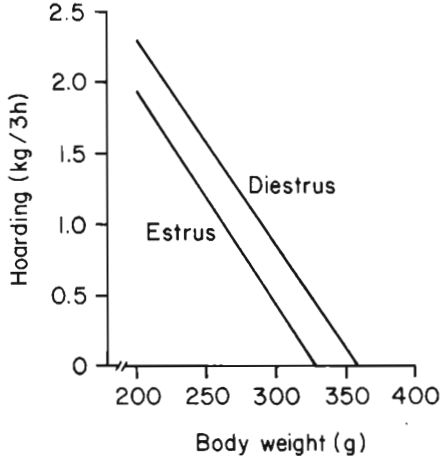



**Figure 4–4.** Effect of body weight on food hoarding at estrus and diestrus for rats that continued to ovulate during periods of food deprivation. The figure shows regression lines fitted to the data (adapted from Fantino and Brinnel, 1986, Body weight set-point changes during the ovarian cycle: Experimental study of rats using hoarding behavior. *Physiol. Behav.* **36,** p. 994. © 1986, Pergamon Press, PLC).

intake and can reverse weight gains in ovariectomized rats (Wade, 1976). The suppressant effect of estradiol on the feeding of ovariectomized rats occurs only if weight is permitted to rise. If weight is kept low after ovariectomy by such measures as adrenalectomy and limited feeding, then estradiol does not suppress feeding (Redick et al., 1973). These considerations support the proposal of Redick et al. (1973) that estrogen, rather than simply acting directly on body weight or feeding, lowers the defended level in a body weight (fat) regulatory system. If weight has already been kept low by other means, then estrogen does not activate effectors. When estrogen changes normally during the reproductive cycle, there is a cyclical rheostasis for body weight, with eating and hoarding among the defense mechanisms brought into action and withdrawn.

## TEMPERATURE RISE DURING THE LUTEAL PHASE OF THE MENSTRUAL CYCLE

Around the time of ovulation, body temperature in women rises by about 0.5°C. The elevated temperature persists during the luteal phase of the cycle and has been used as a guide in birth control. Does this change depend on a change in set-point?

Before answering this question it is necessary to outline Cabanac's (1971, 1979) alliesthesia method of detecting discrepancies between actual and set-point values. *Alliesthesia* is a single word used to indicate that a given external stimulus can arouse pleasure or displeasure depending on the internal state of the body. Negative alliesthesia refers to a decrease in the pleasure, a change from a pleasurable to an indifferent or unpleasant sensation, for example, or from an unpleasant to a very unpleasant sensation. Positive alliesthesia is the reverse process. Alliesthesia refers only to the affective reactions to stimuli, not to whether they are perceived as strong or weak. For example, whether thermal stimuli on the hand are considered pleasant or not depends on internal body temperature. If this is high, then a cool stimulus will be rated as pleasant. If body temperature is low, then the same cool stimulus will be rated as unpleasant. But the accuracy of assessing stimulus intensity is not changed (Mower, 1976).

Cabanac has argued that the pleasure derived from a stimulus depends on the difference between the actual internal state and the set-point designation for that state. This means there are two ways of creating alliesthesia: (1) altering the internal state, or (2) altering the set-point. The basis for thinking that affective reactions are determined by the relationship of actual values to set-point values comes from cases where it is known from other evidence that set-points change. For instance, with fever there are data, quite independent of the alliesthesia method, showing that set-points are higher (Chapter 5). It is assumed from this other evidence that when fever begins the actual temperature is below the now elevated set-point temperature. At this time a previously unpleasantly hot stimulus becomes pleasant (Cabanac, 1969). The other way to

make a previously unpleasantly hot stimulus pleasant is by cooling off the body. In both cases, there is a discrepancy between actual values and set-point values.

In effect then, pleasure is a defense mechanism. It is useful because it guides reactions to external stimuli in a way that will tend to return the internal state to set-point values. According to Cabanac (1971), "Pleasant = Useful."

The advantages of the alliesthesia method for studying set-points are that it is noninvasive, can be used with people, and can be used for different regulated variables, for example for tastes and body weight regulation as well as for thermoregulation. It is technically relatively easy to obtain ratings of affect, but as with self-reports, the usual cautions need to be kept in mind. There is a possibility of observer bias, and of introducing subtle pressures by the experimental instructions and the way they are delivered. Pleasure can also be influenced by past experiences, and this might be a limitation in some cases. Yet there is enough internal consistency and external validation to make this method an extremely welcome tool in the study of regulation. It is entirely appropriate that it should have been devised at the Université Claude Bernard.

Application of the alliesthesia method to the temperature changes during the menstrual cycle suggests that there is indeed a change in set-point. During the follicular phase, when body temperature was below 37.2°C, subjects found that 40°C water was pleasantly warm and that 20°C water was unpleasantly cool. When body temperature was above 37.2°C, the situation was reversed: 40°C water became unpleasantly warm, 20°C water, pleasantly cool. Set-point was therefore estimated at 37.2°C. During the luteal phase, the same procedure gave a set-point of 37.6°C (Cunningham and Cabanac, 1971). The difference between the follicular phase and luteal phase of approximately 0.5°C is consistent with data obtained from measurements of the onset of sweating during exercise or passive warming (Kolka and Stephenson, 1989).

The set-point elevation during the luteal phase probably depends on the increased progesterone. In rabbits this hormone decreases the firing rate of warm-sensitive neurones in the preoptic area and increases the firing rate of cold-sensitive neurones (Nakayama et al., 1975). In some experiments with mammals, progesterone has been found to inhibit the firing of cold-sensitive neurones as well as those of warm-sensitive neurones, but the sample size was very small (Tsai et al., 1988). Progesterone implants in the preoptic area of rats increase their body temperature by 0.5°C (Marrone et al., 1976). Subcutaneous progesterone implants make rats spend more time in the warmer parts of a thermal gradient; their temperature rises by about 0.5°C (Adels and Leon, 1986). However, there are species differences: progesterone lowers the mean body temperatures of blue spiny lizards, *Sceloporus cyanogenys* (Garrick, 1974). Another substance that might contribute to thermal rheostasis during reproductive cycles is interleukin-1; levels of this cytokine are higher during the luteal phase (Cannon and Dinarello, 1985).

The function of being warmer during the luteal phase of the cycle is not obvious. Perhaps it is an inevitable by-product of selective pressures for higher

temperatures at some other stage in reproduction. There is an elevation of body temperature during early pregnancy, and this could well also depend on progesterone (Nakayama et al., 1975). Higher temperatures have also been found in rats during lactation.

## ELEVATED TEMPERATURE DURING LACTATION

Lactating rats maintain body temperatures about 0.5°C warmer than nonlactating females (Adels and Leon, 1986). It has been suggested that this is the result of an elevated set-point because lactating rats in a thermal gradient do not attempt to cool off by selecting cooler areas than nonlactating controls (Jans and Leon, 1983). Progesterone has been implicated in the fever of lactation (Adels and Leon, 1986).

A variety of functions, not mutually exclusive, have been proposed for the higher body temperature during lactation. High temperatures may provide a better physiological climate for milk production, for neural responses necessary for lactation, and for reducing the maintenance needs of the pups by keeping them warmer and so maximizing the energy going into their growth (Adels and Leon, 1986). The most plausible seems to be some function relating to the multiple energetic demands made on the mother, who has to maintain herself, produce milk, and keep the pups warm and growing. In this complex situation there may be an element of conflict between different demands. When given a choice, lactating rats place their pups in a relatively warm area (Jans and Leon, 1983). A warm place for the nest should allow energy to be diverted from maintenance to milk production and growth of the pups. Choosing a warm area may lead to the best bottom-line economy, but it poses a potential problem because when the dam is nursing she becomes warmer; the contact with the young reduces the surface area available for heat loss. One of the stimuli terminating a nursing bout is an elevation in maternal temperature (Woodside et al., 1980). This seldom exceeds 38.25°C when the mother leaves the nest (Leon et al., 1978). Suppose the set-point were not elevated. Then she would have to leave the nest sooner to cool off. One function of thermal rheostasis may be to help resolve this conflict. By having a higher temperature the mother can keep the pups in an economically optimal warm area but still stay with them long enough to nurse them properly.

## EGG COOLING DURING INCUBATION

An example of thermal change with an obvious function is the lowering of body temperature by birds incubating their eggs in very warm environments. Avian embryos do not thrive if they become hot; temperatures of about 45°C are lethal. Rock pigeons, *Columba livia,* manage to keep their eggs at around 40°C, even when the ambient temperature is 45–50°C (Marder and Gavrieli-Levin, 1986). They do this by settling closely on the clutch while at the same time maintaining their own temperatures at ~40°C by cutaneous evaporation. At an

ambient temperature of 50°C, the body temperature of incubating rock pigeons is 2.4°C lower than that of nonincubating birds.

Defense of hypothalamic or brood-patch temperature has not been demonstrated in these circumstances. At milder environmental temperatures the difference between the core temperature of incubating and nonincubating birds is less. Therefore, perhaps brooding prevents the rise in temperature and heat storage that occurs in arid climates (Chapter 5) rather than lowers set-point throughout incubation. In either case, it seems likely that, during heat stress, incubating pigeons regulate at lower levels than nonincubating birds.

## OSMOSTAT RESETTING DURING PREGNANCY

Yet another example of rheostasis associated with reproduction is that of osmoregulation during pregnancy. Plasma osmolality of pregnant women is about 10 mOsmol/kg lower than usual (Lindheimer et al., 1986). The same is true for pregnant rats. The lower plasma osmolality is not caused by any inability to shut down output of antidiuretic hormone (ADH) to minimal levels. In response to injections of hypotonic saline, gravid rats are able to reduce their ADH secretion to levels as low as those in virgin rats (Durr et al., 1981). They are also able to increase ADH production when given hypertonic saline (Fig. 4–5) or when plasma hypertonicity is produced by water deprivation. The ability to respond to osmotic challenges is intact, but the setting of the osmostat (to use

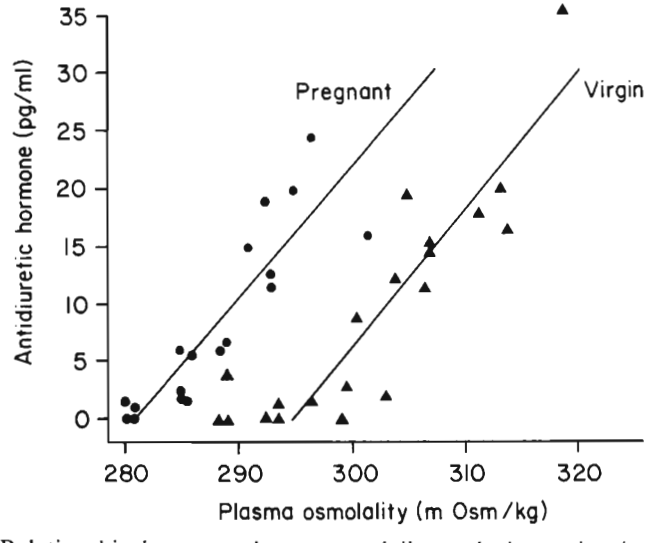



**Figure 4–5.** Relationship between plasma osmolality and plasma level of antidiuretic hormone in pregnant and virgin rats when tonicity was altered by injections of saline solutions of varying concentrations. (Adapted from Durr et al., 1981, *J. Clin. Invest.* 68, p. 341, by copyright permission of the American Society for Clinical Investigation.)

a term found in the literature) shifts downward in pregnancy. Some investigators find a similar, though smaller (5 mOsmol/kg), resetting during the luteal phase of the cycle, but there is no evidence that progesterone is the causal agent (Vokes et al., 1988; see Rollin et al., 1989).

Pregnant rats drink more than usual, but the increase is not enough to account for their hypotonicity; it requires very large amounts of water to overwhelm excretory capacity (Durr et al., 1981). High water intake is doubtless partly related to higher food intake and a need to excrete more solutes. However, drinking thresholds also shift downward during pregnancy (Lindheimer et al., 1986). Brattleboro rats with a hereditary absence of ADH secretion also have lower plasma osmolality when gravid (Durr et al., 1981). Lacking ADH as an effector, presumably they rely on a downward shift in their drinking threshold as the main way to meet the demands of the lowered osmostat.

Why does osmoregulatory rheostasis occur in pregnancy? One suggestion is that the reduction in osmolality is a necessary consequence of the lower plasma $CO_2$ pressures in pregnancy. "The relatively simple process of lowering $P_{CO_2}$ by overbreathing brings a train of physiological consequences" (Hytten and Leitch, 1971). In particular, because $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$, to prevent the pH from rising too much, something must be done to compensate for the reduced $CO_2$. According to Hytten (1968), plasma bicarbonate must be lowered, and along with this lowering of bicarbonate there is a loss of sodium. A downward shift of the osmostat during pregnancy might prevent salt retention mechanisms being activated too readily and so assist in the excretion of bicarbonate and the preservation of pH in the face of lowered $P_{CO_2}$. There are some data consistent with this view: pregnant women on low-salt diets (i.e., with active salt-retention mechanisms) do not lower their plasma bicarbonate as much as those on high-salt diets; their pH is slightly higher than when not eating sodium-depleted food (Lim et al., 1976).

It is certainly desirable to think about how changes in one system impinge upon other systems, and to look for integrative explanations. Nevertheless, in this particular case, the argument is not compelling because pH could probably be defended by ways other than excreting more sodium and lowering osmolality. Simply augmenting the renal retention of chloride ions should be sufficient to prevent too great a respiratory alkalosis developing during pregnancy. It remains to be proved that low $P_{CO_2}$ during pregnancy results in a train of physiological consequences that can be avoided only by lowering osmolality. Whatever the case, the question of why in the first place the $P_{CO_2}$ is lower in pregnancy must be addressed.

## RESPIRATORY THRESHOLDS TO $CO_2$ DURING PREGNANCY

Low maternal $CO_2$ is thought to provide a favorable environment for gas exchange in the placenta and to help the fetus dispose of $CO_2$ (Sjostedt, 1962; Prowse and Gaensler, 1965; Hytten and Leitch, 1971). The fall in $P_{CO_2}$ begins

soon after conception; it anticipates rather than responds directly to the needs of the fetus (Fig. 4–6).

Alveolar $P_{CO_2}$ in pregnant women is about 3–8 mm Hg below the usual values (Goodland et al., 1953; Lyons and Antonio, 1959). The lower $P_{CO_2}$ depends on increased breathing, which in turn depends on increased sensitivity to $CO_2$ (Lyons and Antonio, 1959). Since progesterone administration also lowers the thresholds for ventilatory responses to $CO_2$, even in men, it is possible that this hormone is responsible in part for the downward shift during pregnancy (Lyons and Antonio, 1959), though other factors may also be involved (Regensteiner et al., 1989). It would be interesting to know if there are progesterone receptors in the medullary respiratory centers.

Even though the fall in $P_{CO_2}$ is considered to be an adaptive anticipatory change, the term *overbreathing* is sometimes applied to the mechanism (e.g., Hytten and Leitch, 1971). This is clear enough descriptively and not worth making a great fuss over. It is just another little indication of deeply ingrained, almost hidden, attitudes about constancy of the internal environment. These attitudes are explicit in the following passage:

> Before pregnancy the major preoccupation of the normal body is to maintain internal environmental conditions which are presumably best suited to the functioning of the body in the external environment in which it finds itself. In pregnancy, the same body, living in the same external environment, is subject to a radically different internal environment. If the non-pregnant arrangements are best suited to the functioning of the body, then it follows that a completely changed arrangement cannot equally be best suited to the functioning of the body. We can only assume that the fetus is engineering the changes with its own hormones in the interests of providing what will be the best environment for itself, . . . it is surprising that the average woman tolerates this extraordinary overriding of her own controls with so little visible distress (Hytten, 1968).

This thoughtful passage is worth pondering. It touches on a number of fundamental issues about regulation and rheostasis. However, a lack of "visible distress' is probably not a problem. The study of alliesthesia (Cabanac, 1971) shows that it is a discrepancy between the actual value of a variable and a

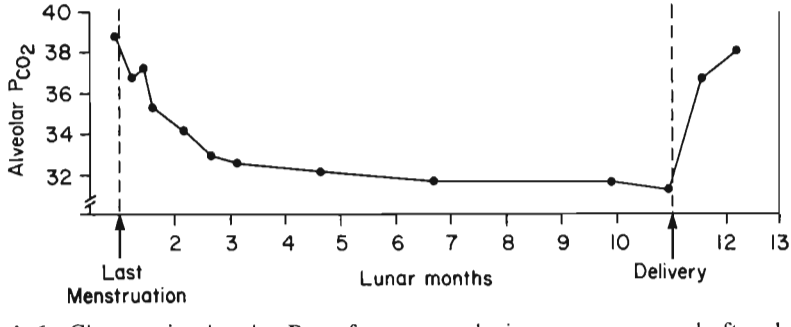



**Figure 4–6.** Changes in alveolar $P_{CO_2}$ of a woman during pregnancy and after delivery. (Adapted from Döring and Loeschcke, 1947, Atmung und Säure-Basengleichgewicht in der Schwangerschaft. *Pflügers Arch.* **249,** p. 441.)

changed set-point, rather than the changed set-point in itself, that produces unpleasant feelings. There is no reason to think that such discrepancies would be allowed to persist for more than a short time. Therefore, to the extent that rheostasis underlies regulatory changes during pregnancy, a lack of visible distress is to be expected.

But one may agree—if evolution is doing its job—that the usual, nonpregnant internal milieu should be the one that is most suited to the functioning of the body. However, if there is a considerable margin of safety (Cannon, 1939) between normal set-points and the levels at which dysfunction occurs, then modest deviations from the usual values need not be more than marginally or temporarily detrimental. All the same, even small disadvantages should be selected against. In this restricted context perhaps a term like *overbreathing* is appropriately applied to breathing during pregnancy. However, the mother is in a conflict situation—a conflict between her immediate needs and the imperatives of contributing to future generations. Rheostasis is an adaptive way of resolving this conflict. The fetus does not simply override the mother's controls. She actively resets them with her progesterone to assist the fetus. In another passage, Hytten (1968) brings out the programmed nature of these changes (which he later also compares to lipostat resetting before hibernation or migration). After noting that traditional research has concentrated on the final stages of pregnancy, he writes:

> Recently our views have changed and we now realize that most of the really dramatic physiological happenings of pregnancy take place in the earliest stages. In this respect, the changes associated with pregnancy differ radically from most physiological adaptations in which the body reacts to a situation by trying to restore homeostasis. In pregnancy the "adaptation" precedes the need, that is to say, the mother makes prior arrangements, often months in advance, to meet situations some of which may never arise.
>
> The variety of changes which appear give the impression of a very widespread interference with normal physiological processes, but it seems more likely, and is biologically much neater, that the changes are all brought about by resetting of controls at a single control centre, namely the hypothalamus.

Clearly, during pregnancy there are classic examples of programmed rheostasis; these probably include numerous other variables besides those described here (see below for speculations on calcium storage).

## RESETTING OF THE GONADOSTAT AT PUBERTY

It has been known for a long time that much lower doses of estrogens are needed in juvenile than in adult rats to eliminate morphological changes in the pituitary following castration (Hohlweg and Dohrn, 1932). The term *gonadostat* was used in 1963 by Ramirez and McCann to describe regulation of estrogen levels. They proposed that the set-point of the gonadostat was altered at puberty so that estrogen was regulated at a higher level, and that this was achieved by a decrease in the sensitivity to feedback from gonadal steroids. When prepubertal female rats are ovariectomized it takes only small doses of

estradiol to suppress the compensatory increase in luteinizing hormone (LH) and follicle-stimulating hormone (FSH). In adult rats it requires much higher doses of replacement hormones to suppress postovariectomy increases in LH (Ramirez and McCann, 1963; Eldridge et al., 1974; Fig. 4–7). Relative insensitivity to negative feedback after maturation can be conceptualized as an elevation in the setting of a gonadostat.

The term *gonadostat resetting* is used operationally here. At one time a given dose of steroid exerts a different degree of suppression of LH or FSH than at another time. The most obvious explanation is that there is some change in the sensitivity of the steroid receptors, or the number of these receptors, in the feedback loop. But it is also conceivable that the sensitivity to steroid feedback remains unchanged. The inhibitory steroid input to a neurone secreting gonadotropin-releasing hormone may be only one of a number of inputs that it receives. If the input from one of these other sources changed at puberty, then a particular dose of replacement hormone given to a castrated animal would have a different effect before and after puberty. Operationally there would be gonadostat resetting, but sensitivity, in the extreme form of the hypothesis of steroid-independent mechanisms, could remain absolutely unchanged. However, it is unlikely that the changes at puberty are entirely a matter of changes in such a steroid-independent pathway. In Figure 4–7, the curves for responses to estradiol are shifted toward higher doses after maturation. If sensitivity of a steroid-dependent pathway remained entirely unchanged, and the changes at

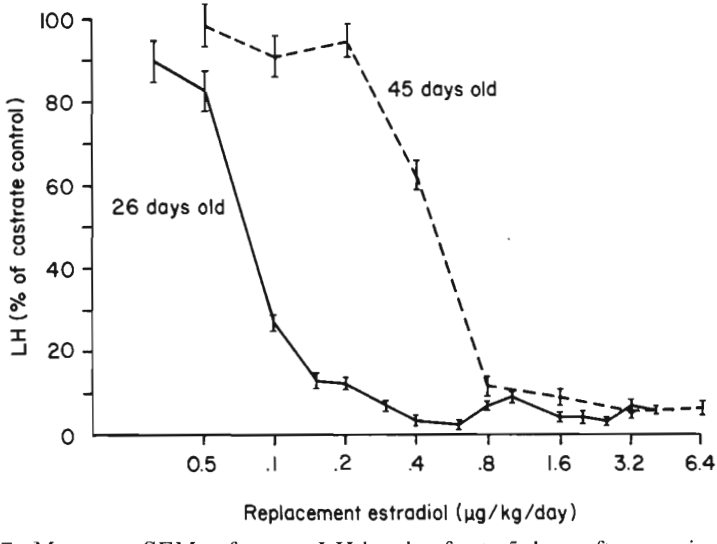



**Figure 4–7.** Means ± SEMs of serum LH levels of rats 5 days after ovariectomy, and treatment with different doses of replacement estradiol. LH is expressed as a percentage of ovariectomized groups without replacement hormone; these reference levels were 372 ng/ml for the 26-day-old group and 346 ng/ml for the 45-day-old group. Rats aged 26 days are prepubertal; rats aged 45 days are postpubertal. (Adapted from Eldridge et al., 1974. Maturation of the negative feedback control of gonadotropin secretion in the female rat. *Endocrinology* **94,** p. 1538. 1974 © by the Endocrine Society.)

puberty were totally accountable by some non-steroid-dependent drive to the gonadotropin-releasing hormone neurones, then in the mature animal there should be a reduced response, but still some response, to doses of replacement hormone to which the immature animal was demonstrably sensitive. The response would be less because of the overriding nonsteroid input (i.e., the slope of the curve would alter), but there should be some evidence of sensitivity. But this is not always the case. At doses of 0.1–0.2 μg/kg/day estradiol (Fig. 4–7), the response is not detectably different from that of untreated animals. The sensitivity to estradiol has shifted toward higher doses. To recapitulate these points: (1) gonadostat resetting is used operationally; (2) even if it were not used in this way, the evidence suggests that there is at least some change in a steroid-dependent pathway; (3) it is not asserted that steroid-dependent changes are the primary or the most important changes at puberty, simply that they are involved somehow in the total picture.

Gonadostat resetting at puberty was first studied in females, but it also occurs in males. A somewhat different method of demonstrating resetting is to implant castrated prepubertal animals with hormone-filled Silastic capsules of sufficient size to maintain testosterone levels just above prepubertal levels, but well below adult levels. It is then possible to follow the time course of LH changes in animals with clamped testosterone levels. It has been found that in rats LH rises between day 47 and day 51, with further increases continuing till at least day 58 (Fig. 4–8; Matsumoto et al., 1986). In intact control animals carrying empty Silastic capsules, large elevations of testosterone occur somewhere between day 54 and day 58, but puberty is a less well defined event in males and testosterone starts to increase even at day 40. Therefore the LH rise in the clamped animals occurs approximately when pubertal changes occur, and this is indicative of an escape of LH from suppression by testosterone. Similar experimental results have been obtained with male golden hamsters, *Mesocricetus auratus* (Sisk and Turek, 1983) and with female sheep (see Karsch and Foster, 1981).

In girls suffering from gonadal dysgenesis, estrogen-replacement therapy suppresses their high gonadotropin levels. Escape from the suppressive effect occurs after a few months or years at about the age when puberty might have been expected. However, it should be noted that the changes in response to feedback might have been influenced by the prolonged administration of estrogen (Kulin, 1985).

Gonadostat resetting is clearly part of the process of puberty, but it is not necessarily the primary event. There is even some disagreement about whether the decreased suppressive effect of estrogen precedes puberty. In some experiments with rats this change has not been detectable until after the initial stages of puberty have begun, that is after the first preovulatory surge of LH (Andrews et al., 1981). It is still possible that some small undetected changes in suppressive effects might have occurred earlier. In other experiments, decreased response to estrogen occurred before puberty (Döcke et al., 1984b). In either case, this is an example of a developmental programmed rheostasis.

With estrogen identified as the feedback signal, it should be much easier to analyze the details of rheostasis in the reproductive system than in the body

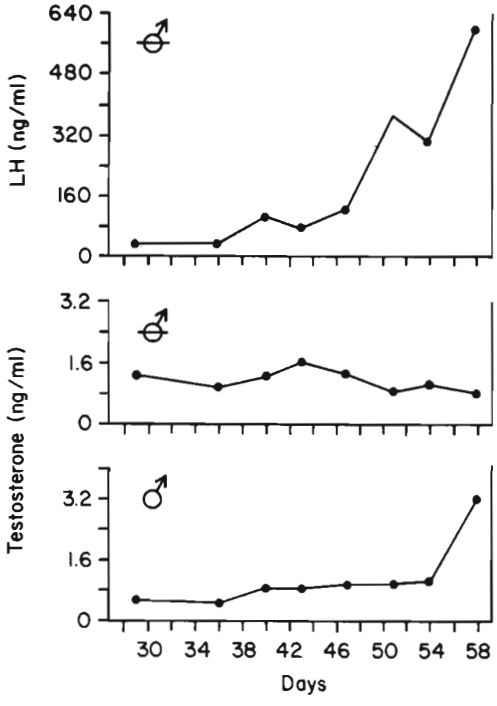



**Figure 4–8.** Serum LH (top) and testosterone (middle) levels of prepubertally castrated rats implanted with Silastic capsules containing testosterone. The testosterone levels remain relatively stable, while the LH levels rise. The lower panel shows the pubertal rise in testosterone in a group of intact rats. (Adapted from Matsumoto et al., 1986, Evidence for activation of the central nervous system–pituitary mechanism for gonadotropin secretion at the time of puberty in the male rat. *Endocrinology* **119,** p. 366. 1986 © by the Endocrine Society.)

weight system, where the regulated variable remains unknown (see Mrosovsky, 1986). Knowledge of the brain areas taking up labeled estrogen provides a useful starting point for researches into the physiological mechanisms promoting and participating in the changes in defended levels. A decrease in the number of estradiol receptors in the medial basal hypothalamus may be part of the story (Day et al., 1987). Changes of this type might be controlled by signals from other hypothalamic areas. The extreme sensitivity of the arcuate-ventromedial nuclei to negative feedback appears to depend in part on influences from the medial preoptic region. At puberty these influences diminish, probably as a result of elevations of estrogen in the preoptic region (Döcke et al., 1984c). A decrease in tonic inhibition from endogenous opiates in the median eminence, starting well before puberty, is probably also involved (Bhanot and Wilkinson, 1983). Chronic (4 days) treatment with morphine greatly enhances steroid suppression of LH output in castrated rats. Without steroids present, morphine has little or no effect on LH. "These data argue for a major role for endogenous opioid peptide-containing neurons in regulating the sensitivity of the hypothalamus to circulating gonadal steroids . . . endogenous opioid peptide neurons may serve as the brain 'gonadostat', and alterations in endogenous opioid peptide release could alter the set-point for the negative feedback of gonadal steroids in LH secretion" (Gabriel et al., 1986). However, gonadostat resetting may be quite complicated, with a switch at puberty from predominantly estrogenic control to dual control by estrogen and progesterone (Andrews et al., 1981).

## SEASONAL CHANGES IN THE GONADOSTAT

Many species become reproductively quiescent over the winter. This change can be analyzed by the same methods as those used to study puberty. For example, when male golden hamsters are kept in short photoperiods, their testes regress. At this time it takes lower doses of replacement hormones to suppress the compensatory increase in LH in castrated animals than when the hamsters are maintained in breeding condition in long photoperiods (Tamarkin et al., 1976). Similar phenomena occur in quail (Davies et al., 1976). In sheep the breeding season is in the autumn not the spring. In this case it is animals in the long days that react more strongly to steroid feedback (Pelletier and Ortavant, 1975; Legan et al., 1977; Lincoln and Short, 1980; Fig. 4–9).

When hamsters are kept continuously in short days, a few months after the initial regression, the testes recrudesce spontaneously. At this time the suppressive effect of testosterone feedback declines again (Ellis et al., 1979). The same also occurs when recrudescence is stimulated by transferring the animals from short to longer photoperiods (Ellis and Turek, 1979). In hamsters the response to steroid feedback changes gradually over a number of weeks. It seems probable that this inertia lies in the mechanisms transducing information about daylength rather than in the gonadostat resetting itself. The gonadostat is capable of rapid resetting, at least in the case of puberty. Apart from this difference in resetting rate, the changes in the gonadostat at the end of the breeding season seem to be the reverse of those occurring at puberty: seasonal cycles are like cyclical puberty (Karsch and Foster, 1981; cf. Berkowitz and Heindel, 1984). From a scientific point of view it is a pity that people are not seasonal breeders. It might have provided an opportunity to learn which of the changes occurring at puberty are hormone dependent and which are associated with social and personal maturation. Perhaps the matter could be studied in a limited way in seasonally breeding monkeys.

It is not argued that puberty and seasonal breeding are the same in every respect (Sisk and Turek, 1983) nor that changes in the steroid-dependent feedback circuit are the only factors in either of these processes (Reiter and Grumbach, 1982). In a variety of species photoperiodic influences on gonadotropins are manifest even in long-term gonadectomized animals. This and other evidence marshaled by Goodman and Karsch (1981) and by Robinson et al. (1985) point to the importance of non-steroid-dependent effects. But the case for such open loop influences (path a in Fig. 4–10; Goodman and Karsch, 1981) does not mean that there are no steroid-dependent effects (path b in Fig. 4–10). There is, in fact, some evidence for the existence of steroid-dependent seasonal mechanisms. First, as with the gonadostat changes at puberty (Fig. 4–7), when data for different doses of replacement steroids are studied there sometimes appear to be actual shifts in sensitivity rather than changes in the amount of response to particular levels of steroids to which animals remain equally sensitive throughout the seasons. For golden hamsters kept in long days, there are some values of testosterone feedback that do not suppress LH or FSH at all in comparison to untreated controls. These same amounts of testosterone do have

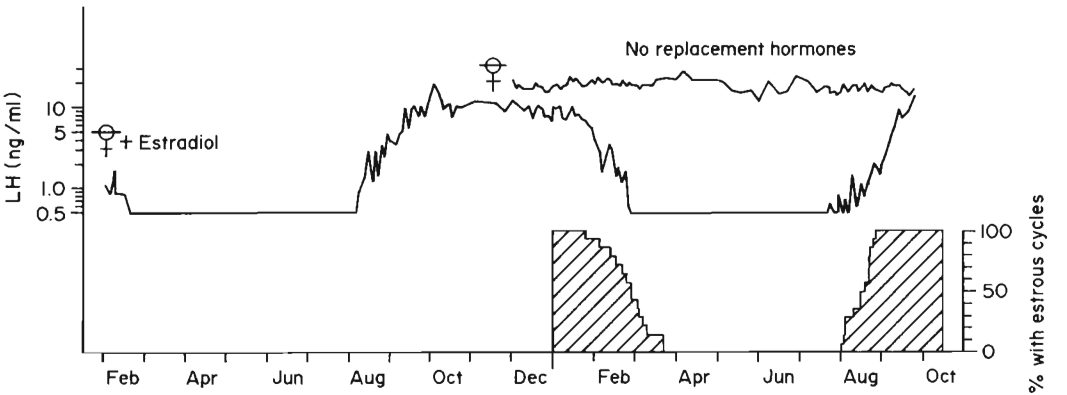



**Figure 4–9.** Seasonal variation in serum LH of ovariectomized ewes exposed to naturally changing photoperiods. One group was implanted with Silastic capsules containing estradiol; these maintained serum estradiol at relatively constant levels (~ 4 μg/ml). Another ovariectomized group was implanted with empty Silastic capsules. The histogram shows the percentage of intact ewes with estrous cycles, and the onset of breeding condition in the fall. (Adapted from Legan et al., 1977. The endocrine control of seasonal jeproductive function in the ewe: A marked change in response to the negative feedback action of estradiol or luteinizing hormone secretion. *Endocrinology* **101,** p. 820. 1977 © by the Endocrine Society.)

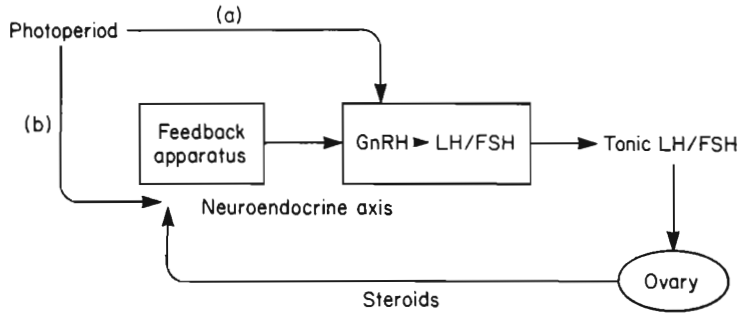



**Figure 4–10.** Two general, not mutally exclusive, mechanisms for photoperiodic control of gonadotropin secretion. (a) Photoperiod directly alters the release of gonadotropin-releasing hormone. (b) Photoperiod alters the response of the neuroendocrine axis to steroid feedback (adapted from Goodman and Karsch, 1981).

suppressive effects in hamsters kept in short days (Turek, 1977; Ellis and Turek, 1979). Admittedly, there is a fair amount of variability in some of these data, and the ability to detect small differences may be compromised, but the evidence from such experiments (see also Sisk and Turek, 1983; Tamarkin et al., 1976, for LH) suggests that a change in sensitivity is part of the mechanism. Second, in ewes there is a temporal dissociation between steroid-dependent and steroid-independent effects over the course of a year (Robinson et al., 1985). As the breeding season ends the LH level in ovariectomized ewes receiving constant amounts of estradiol drops off relatively rapidly, whereas, in ovariectomized animals not given any replacement steroids, a high frequency of LH pulses persists for much longer. LH pulse frequency is the main candidate for a steroid-independent mechanism driving seasonal cycles (Short, 1984). The temporal dissociation between photoperiodic drive in the absence of steroids and the response to estradiol feedback suggests that different mechanisms are involved. Third, for photoperiodic influences on the onset of puberty in lambs, as opposed to those for seasonal breeding in mature ewes, no evidence for a steroid-independent effect has yet been obtained (Foster et al., 1986). There is, therefore, evidence supporting the existence of some steroid-dependent effects. Even if this were not the case, the system behaves operationally as if there were a seasonal resetting of the gonadostat.

There is no evidence in any of the papers cited here that changes in LH clearance rates account for the seasonal differences in response to replacement hormones in castrates. Nor is there any evidence for some general desensitization to steroid hormones or for alterations in steroid-binding globulins. It has repeatedly been shown that the endocrine response to gonadal steroid feedback can change in one direction while behavioral response to the same hormones changes in the other direction. For example, the mating behavior of ovariectomized ewes with standardized levels of estrogen and progesterone is greater when they are kept in short photoperiods (Raeside and McDonald, 1959); in these conditions the suppressive effect of estrogen feedback is less (Legan et al., 1977). In hamsters, testosterone is more effective in restoring copulation in

castrated animals exposed to long days than in those exposed to short days (Campbell et al., 1978; Morin and Zucker, 1978) even though it is in the short photoperiods that the suppression of LH by testosterone is greater. Behavioral and feedback responses to steroids can also be separated by castration (D'Occhio et al., 1985). Seasonal gonadostat resetting is therefore an adjustment in a particular regulatory system rather than a widespread shift in steroid dynamics. Finally, as with so many other examples of rheostasis, the point can again be made that the alteration in regulated level does not represent a breakdown in the system. "Anestrus is not a state of passive non-function, but rather a period of active inhibition of the mechanism controlling tonic LH secretion (Legan et al., 1977)."

## GONADOSTAT RESETTING DURING THE ESTROUS CYCLE

We now turn from seasonal reproductive cycles to estrous cycles. Reactions to steroid feedback also change during these cycles. In the rat the response decreases between metestrus and diestrus (Döcke et al., 1984a). In these experiments the rats were ovariectomized in the morning and had estrogen implanted into the medial preoptic area the same afternoon; blood was then collected for pituitary gonadotropin assay 24 hours later. For studying changes during a 4-day cycle this procedure seems superior to that used by other experimenters who waited 4 days before collecting blood for LH assay (Andrews et al., 1981). In the latter case suppression of LH was similar when ovariectomy and administration of replacement steroids (through subcutaneous Silastic capsules) started at estrus and diestrus but greater when these measures were introduced at proestrus. In both experiments variations in gonadostat setting over the estrous cycle were detected. Having low LH suppression after estrus seems to make more sense in that it allows adequate gonadotropic hormone support for follicle maturation prior to ovulation despite the increasing estrogen at that time (Döcke et al., 1984a). Changes in suppression depend in large part on changes in estrogen levels occurring over the cycle rather than on some intrinsic hypothalamic rhythm that proceeds independently from estrogen levels. Various manipulations of estrogen levels suggest that more estrogen in the medial preoptic area promotes desensitization, and less estrogen there permits resensitization (Döcke et al., 1985).

## THE GONADOSTAT DURING AGING

Plasma LH and testosterone levels are lower in rats 13 months of age than in those 3 months of age. At 13 months a rat is middle aged. Changes at this stage are not likely to result from general nonspecific effects of ill health that are common in old rats (24 months). Lower LH, despite diminished circulating testosterone, stems from an enhanced feedback suppression by testosterone (Gray et al., 1980). This is a clear demonstration of a set-point shift with aging.

There are numerous changes in homeostatic systems during aging, but

many concern the effectors. For example, during heat waves old people are more likely to die; atrophy of sweat glands and decreased ability to pump blood around the periphery result in diminished heat dissipation. An analogous example is the decreased capacity to defend the volume and composition of the extracellular fluid; the kidney is less responsive to challenges to water, calcium, and sodium balance. To risk a generalization, many of the age-related changes in homeostasis are of this kind, a weakening of effectors and a decreased ability to respond to challenges (see Davis and Wood, 1985). Decreased capacity to respond was also evident in the experiments on gonadostat resetting in the 13-month-old rats. In these experiments the rats were first castrated in order to test for the suppressive effects of constant controlled doses of testosterone administered from Silastic capsules. Before the replacement testosterone was given, the castration-induced compensatory LH rise was studied. It was slower in the middle-aged rats. This sluggish response to challenge must be distinguished from the gonadostat resetting, which produces the downward shift in the defended testosterone level (Gray et al., 1980).

Another view is that lower androgens in old age represent a failure to meet an elevated set-point. There are data that fit this view (Muta et al., 1981). For example, in a group of elderly men (mean age 77 years), basal LH levels were higher, and were less depressed by testosterone injections, than in a group of young men (mean age 24 years). Longitudinal studies with several species are needed to discover if there is some consistent pattern in gonadostat resetting with aging.

## CALCIUM STORAGE AND REPRODUCTION

It was argued at the beginning of this chapter that rheostasis is likely to be common where a tissue or substance acts as a reserve. If the level of a reserve were always defended at a particular level, then it could not fulfill its function. Fat is the obvious example, but there may be similar cases.

The skeleton acts as a reservoir of calcium. It also has other functions, especially that of providing structural support. Problems may sometimes arise in fulfilling these functions simultaneously. For flying species especially, there are evolutionary pressures toward reducing weight. The energetic benefits of carrying little fat when a bird is foraging have already been mentioned. Similar considerations apply to bone. However, if the skeleton is already reduced to the minimum sufficient to provide enough strength, then this constrains how much calcium can be mobilized in time of need. For reproduction, much calcium is required both to provision the yolk with calcium so that later the embryo can form bones, and to coat the eggs with shell. The functional considerations have been nicely outlined by Simkiss (1961). Large quantities of calcium are required for the formation of eggshells, but the amount of calcium that can be absorbed through the diet each day is limited. Even on calcium-deficient diets, hens continue to lay for a while, but up to 38% of skeletal calcium can be lost in these circumstances (Taylor and Moore, 1954). This undesirable situation has to be avoided because the hollowed out avian skeleton is

already fragile. "If the skeleton is thus reduced to the minimum weight of material which will withstand the stresses of flight, it is difficult to conceive that it could also act as a store of calcium which in adverse conditions would liberate over 38% of its substance for the production of eggshells. . . . This is putting the problem in its most extreme form, but it demonstrates the conflict between the dual functions of the skeleton" (Simkiss, 1961).

The hen's solution to this problem is to store calcium in advance of eggshell production and to store it in bone specialized for this purpose, the medullary bone, rather than in the normal cortical structural bone. Build-up of medullary bone begins several days before ovulation. Intake of calcium goes up when hens become mature and start laying. The highest values are reached near the time of maximum demand, the calcification of the egg (Mongin and Sauveur, 1979). When hens are given a low calcium mash and a calcium carbonate grit in separate containers, the mash intake on days of egg formation is essentially the same as on days when no eggs are formed, but the intake of calcium grit is more than 5 times higher. Moreover, the hens start to eat more calcium about 6 hours before calcification of the egg (Hughes, 1972). This is not a matter of restoring deficits incurred during calcification of the previous egg, because the specific appetite for calcium also increases before the first egg of a series is calcified (Mongin and Sauveur, 1979).

In rats, increased appetite for calcium lactate occurs after parathyroidectomy (Richter and Eckert, 1937) and is an example of behavioral defense of the internal environment (Richter, 1943). The fact the hens ingest extra calcium before eggshell production actually begins is an indicator that the defended level of the regulatory system is not being met, or in other words, that the setpoint of that regulatory system has been raised in anticipation of future calcium needs. The build-up of medullary bone several days or more before ovulation is also clearly anticipatory.

Perhaps there is an advantage of putting this calcium into medullary bone rather than cortical bone. The calcium store for reproduction can then be adapted for its particular function. During eggshell formation in hens, so great is the demand for calcium that if it were not rapidly mobilized from bone, then blood calcium would be depleted in about 15 minutes (Simkiss, 1967). Medullary bone is especially dynamic; calcium can be rapidly mobilized during eggshell formation and afterwards rapidly restocked for use in future eggs. The number of active osteoclasts in medullary bone increases and decreases during these phases of reproduction (Van de Velde et al., 1984). Although in normal circumstances medullary bone is the main source of calcium for egg production, cortical bone can also be resorbed for this purpose when the birds are fed a calcium-deficient diet (Taylor and Moore, 1954). Possibly the minerals from cortical bone are first transferred to medullary bone. The latter is not so severely depleted when laying hens are kept on a calcium-deficient diet (Taylor and Moore, 1954), another point suggesting that the two types of bone are very different (Simkiss, 1967).

In some reptiles there may not be a need for medullary bone. It has been calculated for the green sea turtle, *Chelonia mydas,* that egg yolk and eggshell

requirements for calcium are spread out enough not to require a rapidly produced mass of mineral (Simkiss, 1961, 1967). Ordinary bone can therefore serve as a store. Female musk turtles, *Sternothaerus odoratus,* lose calcium from their bones. The density of their long bones (which correlates with the mineral content of those bones), falls to values well below those recorded in males during the reproductive season. The bone density in the males remains fairly constant (Edgren, 1960). Perhaps for a turtle supported to some extent by water, a temporary weakening of the bones may be of little consequence, or perhaps during the nonbreeding season these animals are carrying more calcium than they need for structural purposes. This latter suggestion accords with recent information about the alligator, *Alligator mississippiensis* (Wink and Elsey, 1986; Wink et al., 1987). Like musk turtles, female alligators also lose calcium from their bones during the reproductive season. The femur becomes more porous and less robust than in males and non-egglaying females. Maximum porosity is found in animals with eggs in their nests. However, because before egg laying the bones of alligators are relatively dense compared with those of some other species (Table 4–1), they can probably afford to lose considerable calcium without becoming especially weakened. At any rate, no medullary bone has yet been found in alligators, or in turtles.

In other reptiles, however, there is evidently a need at reproduction for calcium stores other than those in normal bone. In certain lizards, the separation of structural calcium and calcium for reproduction is even more complete than in birds. The endolymphatic sacs, bilateral structures that can bulge visibly at the sides of the neck, contain a milky calcareous substance (Ruth, 1918; Simkiss, 1967). The endolymphatic sacs are, in fact, outgrowths of the inner ear. In the Philippine house lizard, *Cosymbotus platyurus,* these sacs can contain as much as 28% of the total calcium in the body (Jenkins and Simkiss, 1968). Several considerations suggest that they have a role in reproduction. The sacs have no obvious structural function. They are said to be less pronounced in males (Ruth, 1918). Also when estradiol is injected into lizards, *Anolis carolinensis,* the sacs become emptier, as judged by diminished opacity to X-rays (Rosenquist, cited in Dessauer, 1974).

Thus there are several kinds of storage tissue, cortical bone, medullary

**Table 4.1.** Femoral Robusticity Index of Various Species

| *Species* | *Robusticity Index*[a] | *Reference* |
|---|---|---|
| Male alligator | 3.8 | Wink and Elsey (1986) |
| Non-laying female alligator | 4.2 | Wink and Elsey (1986) |
| Laying female alligator | 4.3 | Wink and Elsey (1986) |
| Wild rat, female | 4.6 | Riesenfeld (1978) |
| Chicken | 5.2 | Wink and Elsey (1986) |
| Wolf, both sexes | 5.4 | Riesenfeld (1978) |

[a]Note that low values indicate greater robustness because the robusticity index = bone length/$3\sqrt{\text{bone weight}}$.

bone, and endolymphatic sacs, and there are also major species differences in the provision of calcium for egg formation. The general point is that, by analogy with fat storage in anticipation of caloric scarcity, calcium is stored in anticipation of times of extra demand. This storage may involve regulatory systems distinct from those for ionic calcium in the blood. Just as blood sugar remains relatively constant at around 90 mg/dl despite wide variations in the levels of depot fat, so diffusible plasma calcium remains relatively constant at about 10 mg/dl despite the vast export of calcium from bone (or special stores) to the yolk and eggshells. Moreover, the calcium appetite and build-up of medullary bone occur in advance of eggshell production. Perhaps there is some active regulation of mineral storage in bone or special storage tissue.

These ideas recall the work of Nicolaysen (1943) on the stimulatory effects of vitamin D on absorption of calcium from the gut of rats. He found that this effect depended on the state of the skeleton. When bones were deficient in calcium, the absorption-enhancing effects of vitamin D were greater than if the skeleton was saturated and had its normal calcium complement. There may then be some signal (Nicolaysen's "endogenous factor") emanating either from the bone itself or correlated with bone mineralization, that provides information about the state of skeletal saturation. If there is such a signal, then it could well be part of a regulatory loop and be subject to rheostasis.

In his discussions Simkiss (1967) has emphasized that reproduction can be a strain on calcium metabolism. It remains to be discovered to what extent this strain is forced upon the animal each time it reproduces, or whether it has become incorporated into the animal's physiology so that it is handled in a programmed and unstressful way. These considerations are speculative, but they are testable. Would the bone of reproducing musk turtles still become lighter if they were offered abundant supplies of readily assimilated calcium? If so, one might infer that bone resorption depended on a regulated decrease in the long-term calcium store rather than being forced on the animal by the immediate stress of reproduction.

Similar considerations apply to mammals. The lactating rat loses as much as 0.2 g of calcium in her milk each day (Brommage and DeLuca, 1985). During lactation there is a considerable loss of mineral, especially from the ends of the bones rather than from the shafts (Warnock and Duckworth, 1944). For instance, femur ash weights are reduced by a quarter to a third (Brommage and DeLuca, 1985; Miller et al., 1986), and calcium also decreases in other parts of the skeleton. Growth of dentin on the teeth, an index of mineralization, declines (Miller et al., 1985). These changes do not simply stem from inadequate supply of calcium. When lactating rats are offered a high-calcium (1.4%) diet, there is still a loss of bone (Fig. 4–11). This occurs despite the fact that, with this diet, their plasma calcium is elevated to levels close to 12 mg/dl (Brommage and DeLuca, 1985). There is calcium available right in the animal's blood stream, yet it mobilizes minerals from bone. If extra calcium is made available in a solution, throughout most of the duration of lactation mother rats do not drink more of it than they do before pregnancy. But when they are fed a calcium-deficient diet, they do drink more of the calcium solution (Woodside and Millelire, 1987). Thus, rats eating a regular diet during lactation do not act as

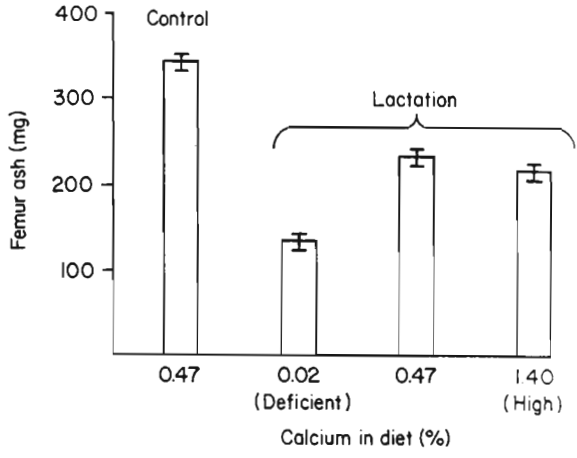



**Figure 4–11.** Femur ash weight of lactating rats as a function of dietary calcium (mean ± SEM). The nonlactating control group was composed of both rats that did not deliver and rats that had their pups removed (adapted from Brommage and DeLuca, 1985).

if they were deprived of calcium. One presumes that bone mass declined during lactation in these last studies as in those cited previously. Ideally measures of bone mineralization and intake of calcium solution should be combined in the same experiment.

A programmed loss of calcium in lactation, evident in animals fed high-calcium diets, does not imply that all bone loss during lactation is programmed. Depending on the diet, and on the number of pups in the litter (Peng et al., 1988), bone might be reduced below programmed levels. Both programmed and imposed calcium loss need not be a major strain on an animal's physiology if there is also a programmed build-up of calcium during pregnancy. In pregnant rats bone formation accelerates; total femur calcium rises (Miller et al., 1985, 1986). In young human mothers calcium balance becomes more positive than in nonpregnant controls. Increased calcium build-up begins by weeks 25–29 of pregnancy, that is before the fetal skeleton becomes mineralized. It is an anticipatory adjustment (Heaney and Skillman, 1971) because later, during lactation, at least in some circumstances, bone mass decreases in women (Wardlaw and Pike, 1986). Again, it is possible to test whether calcium storage in pregnancy depends on elevation of some set-point. What would happen in animals if a period on a calcium-deficient diet were imposed during the middle of pregnancy? Would they compensate afterwards by increased calcium intake, and would they catch up in storage to the elevated levels that would have occurred if they had not spent those days on the deficient diet? But perhaps the best preparation for testing for regulation of calcium stores would be the endolymphatic sacs of lizards, where the anatomically separate store offers scope for physiological interventions.

## CYCLICAL OSTEOPOROSIS AND ANTLER GROWTH

It is not exclusively females that need calcium for procreation. Males of species with antlers need calcium too. Analysis of specimens of mule deer (*Capreolus capreolus*) collected throughout the year reveals that the porosity of skeletal

bones is inversely related to that of the antlers (Brockstedt-Rasmussen et al., 1987). Some of the mineral deposited in the antlers of white-tailed deer (*Odocoileus virginianus*) comes from their bones (Cowan et al., 1968). Just as seasonal fat deposition precedes hibernation and migration, so seasonal calcium accumulation in the bones provides a reserve for antler formation. Perhaps both are regulated processes. Banks et al. (1968a, b) found that the bone of mule deer was most depleted when antler growth was maximal. These experiments are notable because they were conducted with captive animals fed *ad libitum*. Although they have been criticized for their small sample size and possibly traumatic biopsy procedure (Brockstedt-Rasmussen et al., 1987), these experiments strongly suggest that mineral loss from skeletal bone is not forced upon the animal but is programmed. It took place "even though high quantities of these minerals were available through the diet" (Banks et al., 1968a). However, tests of defense and further experiments are needed. For instance, calcium should be available in a form separate from other food, lest there are constraints on how much deer can eat when ingredients are mixed. Banks et al. (1968a) note that, although there are some similarities to clinical osteoporosis, cyclical osteoporosis in deer is physiological.

## A BONE MECHANOSTAT

So far the discussion of bone has been devoted to its role as a calcium store for reproduction. How bone is built up to be sufficiently strong and mineralized to fulfill its structural role has not yet been considered. According to one formulation (Frost, 1987), this depends on a minimum effective or threshold strain. When the bone is subjected to strains above this threshold, changes in mass and architecture are initiated until its strength becomes such that minimum effective strains are not exceeded. A single excessive strain does not trigger the full response. Rather, it is the usage over some longer time span that is integrated. For instance, "all mechanical forces and motions imposed on bone by the subject's typical weekly physical activities" (Frost, 1987) go into determining whether the minimum effective strain has been exceeded. If that is the case, then strengthening of bone is initiated. Conversely if the minimum effective strain is not surpassed, then architectural changes occur that result in a weakening of the structure. The system has a large safety margin in that "conscious subjects cannot voluntarily make mechanical bone strains exceed a threshold value of about 1/10 the fracture strain" (Frost, 1987). The system exhibiting these properties has been called the *mechanostat* (Frost, 1987).

It is not evident that this is more than a redescription of hypertrophy and atrophy through use and disuse. Nevertheless, the matter is worth noting in a review of rheostasis because there is a second part to this proposal, namely that the minimum effective strain, or set-point for strength, can be altered by circulating agents. For instance, it is suggested that at menopause the mechanostat becomes less sensitive to strains actually impinging on the bone. This produces the impression that the bone is not being subjected to strain. A state of apparent absence of strain initiates weakening of structure. As bone mass

decreases, the actual strains build up. Eventually the mechanostat, even though insensitive, detects that there are strains present and halts further bone remodeling. In terms of strains, one can think of this as a raised set-point, a greater strain on the bone being required before its mass stabilizes (Frost, 1987). If the forces impinging on the bone remain the same before and after menopause, then greater strains are reached only when the bone is weaker. In terms of the strength of the bone, one can think of the lowering of set-point at menopause. These two ways of conceptualizing the set-point change arise because the signal depends on a combination of forces impinging on the bone and its strength. It is not a matter of regulating a purely internal variable like the plasma level of a hormone.

Again it is not made evident that this account is superior to others. Evidence of defense of different bone strengths is not provided. Perhaps effector mechanisms are deficient. As a model of menopause, would an ovariectomized rat be capable of showing compensatory increases in bone mass after a period on a calcium-deficient diet? The discovery of estrogen receptors on cultured human osteoblast-like cells gives life to the possibility that estrogen directly promotes bone formation (Eriksen et al., 1988) rather than affecting some higher-order system. Nevertheless, with bone having both structural functions and estrogen-modulated calcium storage functions, the idea that interactions between the relevant regulatory system might occur at some higher level like a mechanostat, rather than as a direct confrontation over the osteoblasts and osteoclasts, is consonant with what seems to happen in a number of other cases of regulatory conflict.

## HIBERNATION

The body temperature of mammalian hibernators provides one of the most striking examples of rheostasis, both for the extent of the changes in regulated levels and for the speed with which adjustments can be made. It is also remarkable how slowly this came to be appreciated. For a long time the low temperatures during torpor were thought of as evidence for defective thermoregulation. Bernard's (1878) belief that mammalian hibernators, like plants, were overcome by cold has already been mentioned (Chapter 1). This general attitude persisted, so much so that poor thermoregulation was considered necessary for hibernation. As a review in 1931 (Johnson) explained, "a fact which must be kept in mind is that a poorly developed heat regulatory mechanism is a prerequisite to the ability of a mammal to hibernate." Thirty years later, in his book *The Physiology of Natural Hibernation,* Kayser (1961) was still using words like "insufficient," "defective," and "little developed" to describe the thermal abilities of hibernators, even though his own researches had uncovered a number of facts that could be equally well interpreted as indicative of good thermoregulation, and even though he was aware that arousal from hibernation, when an animal warms itself from 5° to 37°C in a few hours, requires a spectacular heat production. As late as 1968, Hammel et al. wrote, "we cannot conceive that the intrinsic 'set' temperature of the hypothalamic regulator has been decreased from its euthermic level to a hibernating level from which level

any deviation will activate the appropriate thermoregulatory response." Although some of their own records showed increases of oxygen consumption following small drops in hypothalamic temperature, they chose to interpret these as intermittent activation and inactivation of arousal from hibernation. Rather than accept evidence for an active and continuous regulation of temperature during hibernation, Hammel et al. (1968) resorted to the idea of a metastable state in which temperature holds relatively constant as a result of repeated but aborted arousals.

Even at that time, however, there were numerous facts available that accorded well with a lowering of the thermostat setting during hibernation. Data were available showing that body temperatures of torpid animals are often a little above ambient levels. In some cases the differences are a few °C, too much to be maintained by passive processes. In other cases the excess temperatures are small. However, variations of skin temperature and muscle tone suggest that vasomotor activity and muscle tone contribute toward constancy in deep body temperature (Strumwasser, 1959). Also, drugs that interfere with thermoregulation in normothermic animals reduce the difference between body temperatures and ambient temperatures during hibernation. Instances exemplifying these and other points were collated and reviewed in 1971 (Mrosovsky). It was concluded that physiological virtuosity was more likely than defective thermoregulation. Many of the facts were consistent with Strumwasser's (1960) conclusion that hibernation involved "an extension of already available mammalian regulatory mechanisms for operation at low temperatures." However, the obvious tests for thermoregulation during hibernation had not been performed. These were to alter the temperature of the thermosensitive region of the hypothalamus by local heating or cooling and watch for activation of thermal defenses.

Even when some of the first experiments with thermodes implanted into the preoptic region of hibernators were done, and some increases in heat production were obtained in response to hypothalamic cooling, these were interpreted as "sudden reactivation" of thermoregulatory systems that were otherwise "completely inactive" in deep hibernation (Heller and Hammel, 1972). However, other researchers, using similar methods, concluded that the capacity to thermoregulate without arousing was present during hibernation (Hartner et al., 1971; Mills and South, 1972). They were particularly impressed by the reaction of one of their marmots to hypothalamic warming. This animal moved out of its nest and uncurled itself from the normal hibernating posture. Later, after preoptic warming had ended, it crawled back into its nest and continued hibernating without arousing. Other data showed increased heart rate, but without electromyographic activation, in response to hypothalamic cooling. The intensity of the heart rate response varied with different thermal stimuli, indicating that it was a thermoregulatory response rather than a non-specific one (Mills and South, 1972).

Finally, in the early 1970s, almost 100 years after Bernard had written about the absence of a mechanism for maintaining thermal constancy in hibernating mammals, it became generally accepted that indeed there is such a mechanism and that it is probably the same one that operates when the animal

is normothermic. The most compelling evidence for this is that if the preoptic area of a deeply hibernating animal is cooled below a certain threshold (or set-point), then heat production increases in proportion to the amount the temperature is reduced below that threshold (Fig. 4–12). The phenomenon is similar to that seen in normothermic animals (cf. Fig. 5–5), but the threshold value is much reduced. Proportional control and lowered thresholds have been demonstrated both in hibernating marmots (*Marmota flaviventris*; Florant and Heller, 1977) and in ground squirrels (*Spermophilus lateralis*; Heller and Colliver, 1974). Marsupials evidently also thermoregulate during torpor (Geiser, 1986).

Many of the bursts of heat production seen in previous experiments with ground squirrels (Hammel et al., 1968, Heller and Hammel, 1972) have now been reinterpreted as responses proportional to the discrepancy between the actual and the set hypothalamic temperature (Heller and Colliver, 1974; see also Mrosovsky, 1971). It has also been discovered that during entry into hibernation the set-point is lowered from about 37° to 5°C in a gradual manner (Florant and Heller, 1977; Heller et al., 1977). Manipulating hypothalamic temperature through the same thermode, implanted in a fixed position in the same individual, elicits qualitatively similar thermoregulatory responses in normothermic animals, during deep hibernation itself, and during the transitional state of entry to hibernation when the set-point slides from its normothermic level to its hibernation level. Even the quantitative difference, the decreased responsiveness (decreased proportionality constant) of the system in hibernation, has a $Q_{10}$ of 2.5 (Florant et al., 1978). The obvious inference is that the same controls operate over an approximately 30°C range of temperature but obey the usual laws depressing biological processes at low temperatures. "Clearly, then, hibernation is a state in which the mammalian regulator . . . is reset to a lower level, and it is not a state during which the thermoregulatory system is inactivated" (Heller et al., 1977).

Why did it take so long for this to become evident? Perhaps thought became a prisoner to certain theoretical formulations about thermoregulation and the actual data were neglected, but there are also characteristics intrinsic to the phenomenon of thermal rheostasis in hibernators that make it elusive, in particular the speed with which thermostat resetting can take place. The low thermal set-point during hibernation can indeed be defended by proportional responses, but it also remains true that the thermostat can be rapidly reset

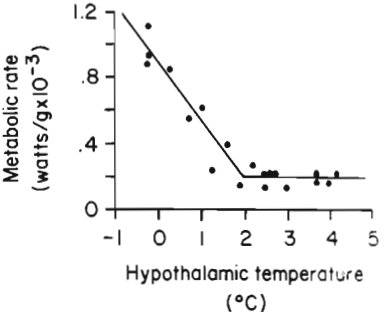



**Figure 4–12.** Metabolic heat production of a golden-mantled ground squirrel hibernating at an ambient temperature of 3.5°C. Hypothalamic temperature was manipulated by cooling the preoptic region (adapted from Heller and Colliver, 1974, *Am. J. Physiol.* **227,** p. 586).

upwards during an arousal or a partial arousal. Hypothalamic cooling sometimes initiates such arousals. When this happens, the increased heat production can be turned off by stopping the cooling and warming up the hypothalamus instead. However, the hypothalamus must be warmed to a higher temperature than that prevailing before the cooling was begun (Fig. 4–13; Heller and Hammel, 1972). This suggests that cooling can result in a rapid upward shift in the defended level, i.e., it initiates an arousal or a partial arousal. Once the arousal has progressed and the body temperature has increased considerably (e.g., >20°C), it may require hypothalamic temperatures >37°C to suppress arousal (Heller and Hammel, 1972). Thus, both cooling and warming (or the associated physiological and behavioral activation) can result in upward shifts in the set-point (cf. Florant and Heller, 1977).

Furthermore, the set-point can change spontaneously within a bout of hibernation. In marmots it drops a degree or two during the first 2 days of a bout, and then appears to rise again during the last 2 days (Florant and Heller, 1977). Just before an arousal the set-point, as determined by measuring the proportional responses to hypothalamic cooling, can be higher than the actual hypothalamic temperature (Florant and Heller, 1977). Perhaps this is the result of a slow response, or a very small response when the proportionality constant is depressed by low temperatures. Whatever the reason, if differences between the actual and set temperatures can arise, it may make detection of proportional responses harder. For instance, if the hypothalamus were warmed a little at a time when the set temperature is already above the actual temperature, then no decrease in heat production would be seen. Conversely, if the hypothalamus were cooled a little at a time when the set temperature is already below the actual temperature, then no increase in heat production would be seen. During the entry to hibernation, experimental cooling of the preoptic

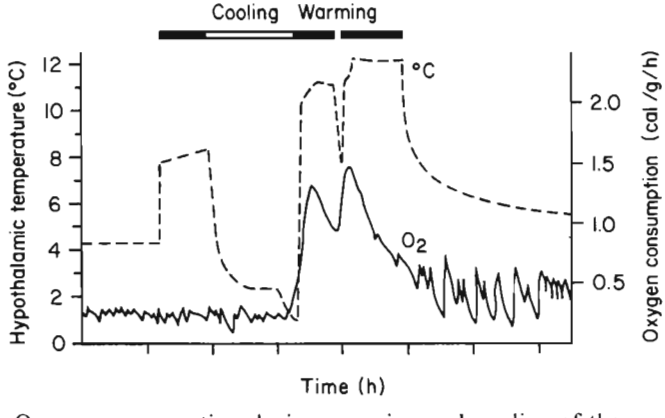



**Figure 4–13.** Oxygen consumption during warming and cooling of the preoptic region of a golden-mantled ground squirrel during hibernation. Ambient temperature was ~ 3.5°C. (Adapted from Heller and Hammel, 1972, CNS control of body temperature during hibernation. *Comparative Biochemistry and Physiology* **41A**, p. 354. Copyright 1972, Pergamon Press, PLC.)

region by as much as 4.5°C below its unmanipulated level sometimes fails to elicit increased metabolism (Florant and Heller, 1977). Not enough is known about the circumstances permitting actual temperature to be above the defended level. It is clear, however, that such discrepancies can develop, that the set level can change rapidly, and that it is not always stable over a bout of hibernation. The very plasticity of the hibernator's thermoregulatory system makes it hard to study its operation in a particular state.

Some of these complexities might be responsible for cases where proportional responses were not detected in ground squirrels (Heller and Hammel, 1972), or at all in individual chipmunks, *Tamias striatus* (Pivorun, 1986), or in marmots during the first few days of a hibernation bout (South et al., 1975). There may be a stage at the start of hibernation when the set-point to be defended has not been fixed; changes in ambient temperature during this time may result in a change in set-point (South et al., 1975). To the extent that ambient temperature can determine the set-point (Mrosovsky, 1971), it makes for a curious, perhaps questionable and certainly elusive kind of thermoregulation. Probably another important variable is how much the set-point is above the temperature that triggers an arousal, the *alarm temperature*, as it is sometimes called. If the two are close, then only slight hypothalamic cooling can be used if an arousal is to be avoided. Failure to detect proportional responses might also reflect a greater role for skin thermosensors in the temperature regulation of some species or individuals (Pivorun, 1986). It is also possible that there are indeed occasions when thermoregulatory systems are inactivated in hibernators. But it is now clear that often temperature is regulated during hibernation and that the defended level changes gradually over a wide range during entrance to hibernation and can rise abruptly during an arousal. That such a splendid example of rheostasis should once have been thought inconceivable might perhaps soften attitudes toward some of the speculations about rheostasis in this book.

There still remain some questions about the adaptive value of lowering set-point during hibernation. Energy conservation could be achieved simply by turning off the thermostat and letting temperature fall passively. A comparison with a budget-conscious householder may be appropriate. When leaving a house in the winter, it is safer to turn the thermostat down rather than off lest the pipes freeze in a sudden cold snap. Freezing to death is one of the hazards of hibernation. If temperature drops too fast, then hibernators are overwhelmed (Pengelley and Asmundson, 1970). Having the alarm temperature set several degrees above zero might allow sufficient margin to initiate an arousal before being overcome. An alternative, more economical way to avoid freezing would be to maintain a temperature a few degrees above a very cold ambient level. There are, in fact, numerous examples of hibernators not arousing in near zero, or even sub-zero, conditions but instead increasing their metabolism and the temperature difference between their bodies and the environment (review in Mrosovsky, 1971). It may also be that, given the existence of a thermoregulatory system, extending the range over which it operates is simply a more likely path for evolution to take than devising an additional alarm system that

turns on at a critical level (note the assumption here that hibernation is an advanced adaptation rather than a primitive relic). Indeed, it has been suggested that the alarm temperature does not exist as a separate mechanism but is an expression of the operating characteristics of the normal system at very low temperatures where the open loop gain becomes large (South et al., 1975). Ability to alter set-points rapidly could also provide economies: if disturbance does not persist, an arousal may be aborted and the cost of rewarming all the way to 37°C avoided (Pivorun, 1986).

## ACID-BASE STATUS IN HIBERNATION: ALPHASTAT RESETTING

Mammalian hibernators provide yet one more example of rheostasis. Their sliding and climbing set-points for weight have been described earlier in this chapter. Their thermal behavior corresponds to a resetting of the hypothalamic thermostat. "The same kind of resetting probably occurs for acid-base regulation" (Malan, 1985). This resetting illustrates a number of interesting points about regulation, including regional differences for different parts of the body, and how matters can appear in a new perspective with a deepening appreciation of the nature of the regulated variable. The account here is based on expositions by Reeves (1985) and Malan (1985).

At first glance it may seem odd to talk of resetting of acid-base regulation in hibernation because pH remains almost unchanged in the torpid animal (data reviewed by Malan, 1985). However, the regulated variable is probably not pH but the fraction (alpha) of total histidine imidazoles (Im) that are unprotonated.

$$Im + H^+ = HIm^+$$

$$alpha_{Im} = \frac{Im}{Im + HIm^+}$$

Why are these histidine imidazoles so important? Of the amino acids constituting proteins, histidine has properties that make it especially suited for acid-base regulation. In particular, the imidazole side chains attached to the alpha carbon atom bind protons. However, when the pH is close to 7 the affinity for protons is relatively weak, so that only about half the imidazole rings are protonated. Other amino acids do not possess this reversible kind of proton binding in the physiological range. Therefore, histidine imidazole is the most important protein buffer.

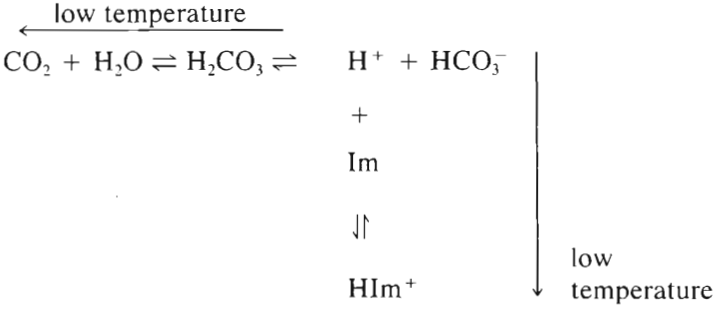
Two further aspects of this protein buffer system are of particular importance: the functional consequences of protonation and the thermal characteristics of the system. Adding a proton to the imidazole ring alters the charge of the protein, and this in turn changes its conformation. The enzymatic functions of these proteins are "exquisitively sensitive to these alterations in histidine imidazole charge state" (Reeves, 1985). So there is a good reason for maintaining constancy in the fraction of imidazole groups that are unprotonated (see also Somero and White, 1985).

The thermal characteristics of the imidazole buffer system make it particularly suited for maintaining this proton balance. In particular the dissociation constant of $ImH^+$ falls considerably as temperature declines. In itself this would not maintain but increase imidazole protonation at low temperatures. However, the effect of temperature on the imidazole buffer system should not be considered in isolation. It takes place in the context of thermal effects on other buffer systems, in particular the $CO_2$–bicarbonate system:

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

When temperature falls, water dissociates less. Because of this, and various other facts of physical chemistry, considering the $CO_2$-bicarbonate system in isolation, there is a tendency for pH to rise as temperature decreases.

Considering these two buffer systems together, low temperatures are working in opposite directions with respect to the protonation state of imidazoles:




The dissociation constants of the systems involved, and their changes with temperature, are such that the fraction of unprotonated imidazoles ($alpha_{Im}$) remains the same at different temperatures. However, while cooling does not affect the $alpha_{Im}$ ratio, it does reduce the amount of $H^+$. "The salient feature of this analysis is recognition of the fact that *normal* acid-base status requires a different set of pH and $P_{CO_2}$ values *at each temperature*" (Reeves, 1985). Turning this statement around, when the pH remains the same at different temperatures, there must be changes in acid-base regulation with respect to $alpha_{Im}$. This brings us back to mammalian hibernation.

The pH during hibernation, as has been mentioned already, is similar to that in the normothermic state. Therefore, there must be a lower fraction of unprotonated imidazoles. But how do we know this is a regulated change rather than something imposed on the animal by its hypothermic state? Malan (1985) gives a number of reasons for thinking that there is active regulation of acid-base status during hibernation. To start with, hibernation is thought to be a relatively recent adaptive strategy that evolved separately in taxonomically varied groups of animals. It is unlikely, therefore, that there are fundamental differences between hibernators and nonhibernators in their biochemical or-

ganization (see also Mrosovsky, 1971). In nonhibernators when the blood cools and warms, as it does when it flows from the core to the cooler periphery and back again, the pH changes. Therefore to produce a constant pH (and a reduced $alpha_{Im}$) during deep hibernation, there must be some other factor at work in the hibernators. This other factor is respiration. In the whole animal the buffering mechanisms are not isolated closed systems. The pH in the normothermic state is maintained in a suitable range for $alpha_{Im}$ constancy by ventilation and other processes. Sensitivity to changes in $CO_2$ remains during hibernation. For example, the periods of apnea of hibernating hedgehogs at first shorten and then disappear with rising $CO_2$ concentrations in the inspired air. These responses occur before body temperatures increase (Tähti, 1975). Moreover, in most studies the variation of pH and $P_{CO_2}$ has been similar in hibernation to that in the normothermic state (see Malan, 1985). This again suggests that regulatory mechanisms are equally effective during hibernation. But since pH is higher during hibernation, these regulatory mechanisms are maintaining a lower than normothermic $alpha_{Im}$. This state is achieved by reducing ventilation and allowing blood $CO_2$ to rise by just the right amount.

Perhaps the clearest evidence for active regulation of acid-base balance during hibernation is the considerable increase in respiration at the start of an arousal from hibernation (Malan et al., 1988; Bickler, 1984). Tidal volume goes up even before temperature rises. This means that acid-base status is not imposed on the hibernator simply by the temperature characteristics of the various biochemical reactions involved. Rather, at the start of an arousal, at an unchanged temperature, the hibernator can switch from regulating at reduced $alpha_{Im}$ (with constant pH) to regulating at normal $alpha_{Im}$; i.e., the setting of the alphastat changes at the start of an arousal.

However, the situation during hibernation is more complex than a unitary lowering of the alphastat. Everything that has been said so far applies to pH and $alpha_{Im}$ values for blood only. In the cells of certain tissues, the heart and the liver, the alphastat remains constant during hibernation (Malan, 1985; Malan et al., 1988). It does not seem unrealistic to think there could be numerous detectors for the ratio of histidine imidazoles that are unprotonated. If the charge on proteins is so important in their effectiveness as enzymes, then a detector could be sensitive to the biochemical consequences of enzyme-activated reactions. There could be intracellular detectors, and these might differ in different tissues. But how alphastats could be reset during hibernation in some tissues but not in others is a challenging question.

The biological function of lowering $alpha_{Im}$ in hibernation is equally problematic. It has been suggested that the accumulation of $CO_2$ (an effector mechanism supporting the lowered alphastat setting) contributes to lowering of temperature both directly by inhibiting metabolism and indirectly by turning down the thermostat (Malan, 1985; Malan et al., 1988). However, as thermal setpoints can change in so many different circumstances (Chapter 5), there seems to be no compelling reason for the resetting during hibernation to require $CO_2$ accumulations, though this might still be the case. The regional differences in acid-base regulation during hibernation are also puzzling. There have been some general pronouncements about the heart and the liver being particularly

important tissues, but inadequate development of convincing arguments as to why cells in these organs should not show lowered $alpha_{lm}$ during hibernation.

## SLEEP AND SHALLOW TORPOR

The link between hibernation and sleep has been considered since ancient times. During deep hibernation itself, the amplitude of electrical activity in the brain is so reduced that it is impossible to distinguish the different types of sleep with any confidence. During entry to hibernation and shallow torpor, with body temperatures around 27°C, the electroencephalogram shows a high percentage of activity with characteristics of slow wave sleep (Heller and Glotzbach, 1977; Walker et al., 1979). Thresholds for metabolic heat production in response to hypothalamic cooling have been measured during slow wave sleep in kangaroo rats, *Dipodomys ingens*, and found to be lowered (Glotzbach and Heller, 1976). The mean decrease of 0.3°C is small and less obvious than the decrease in responsiveness (proportionality constant) but is nevertheless consistent with the idea that the set-point is lowered during slow wave sleep. A lowered set-point in both hibernation and sleep, together with the large amounts of slow wave sleep in shallow torpor, is consistent with the view that hibernation is an extension of sleep.

## SLEEP AND $CO_2$ PRESSURES

In addition to changes in thermoregulation during slow wave sleep, there are changes in the regulation of blood gases. Arterial and alveolar $CO_2$ pressure increase slightly (ca. 5 mm Hg). This probably depends on a decreased sensitivity of chemoreceptors in the medullary centers. When dogs breathe air containing 1–3% $CO_2$, their ventilatory response is still present during slow wave sleep, but the threshold is higher than when they are awake (Fig. 4–14; Phillip-

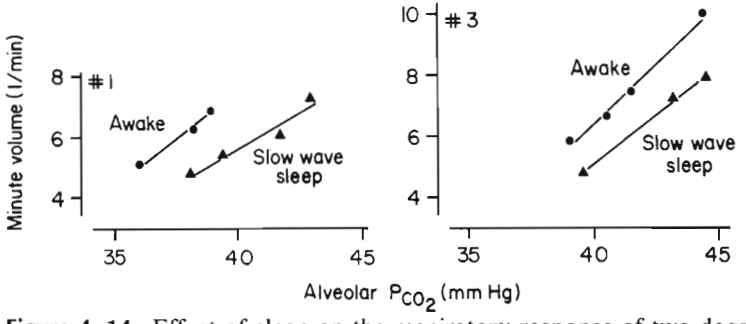



**Figure 4–14.** Effect of sleep on the respiratory response of two dogs to increasing alveolar $CO_2$ pressures (adapted from Phillipson et al., 1976, *J. of Appl. Physiol.* **40,** p. 690).

son et al., 1976). In some experiments there is also a reduced slope of the function relating the ventilatory response to $P_{CO_2}$ (e.g., Sullivan et al., 1979).

## CIRCADIAN TEMPERATURE RHEOSTASIS

Sleep has been extensively studied as a variable showing endogenous circadian rhythms. Given the lowering of thermal set-point during slow wave sleep, one would expect there to be a circadian temperature rhythm. However, temperature rhythms are not merely consequent on sleep or activity but are also programmed on an independent circadian basis. For instance, there is a lack of temperature drops during afternoon naps (Geschickter et al., 1966) and a persistence of temperature rhythms in sleep-deprived people (review in Aschoff, 1970). Even when subjects are awake during tests, they respond differently to thermal challenges at different times of day. For example, when immersed in a 30°C bath, there is a smaller fall in core temperature during the early part of the day than in the afternoon or evening (Cabanac et al., 1976). Set-points estimated from the core temperature at which thermal stimuli shift from being unpleasant to pleasant show daily amplitudes of about 0.7°C (Cabanac et al., 1976). There is a similar daily amplitude in the body temperature thresholds for sweating (Stephenson et al., 1984). In pigeons, *Columba livia,* amplitudes of daily body temperature rhythms are greater, often as much as 4°C. It has also been shown that these cycles are not merely a consequence of the birds being asleep at certain times. Even in awake pigeons the thresholds for heat production in response to cooling thermosensitive parts of the brain are lower during the dark portion of the cycle (Heller et al., 1983). Finally, studies on the mechanism of circadian temperature rises support the view that these are regulated events. Prostaglandins are known to mediate the set-point elevations during fever (Chapter 5). It has now been shown that prostaglandin synthesis inhibitors (antipyretic drugs such as sodium salicylate and indomethacin) decrease temperatures of rats more effectively at night when their temperatures are normally higher than during the daytime (Scales and Kluger, 1987; see also Scales et al., 1988). These and other findings support Aschoff's (1970) assertion that "core temperature is a regulated quantity, and its diurnal oscillations are nothing else than regular shifts of the set-point." The influence of activity can be considered as a load on the system.

However, a challenge to the idea of a cyclic shift in thermal set-points has come from Briese (1985). He found that rats, given an opportunity to move about in a temperature gradient, preferred to be in a cool area during the night, when they have higher body temperatures. During the day, when they have lower body temperatures, they went into warmer places. Since the behavioral and autonomic defenses appeared to be working in opposite directions, Briese rejected the idea of a simple shift in set-points. It is not necessary to do so. There is still a cycle in body temperature in the rat. It may be that there is also a shift in the particular behavioral responses appropriate for defense of the set-point even though the set-point changes. At night, when the rat is awake, it may be acceptable to be in a relatively cool place; perhaps it even helps to

prevent the animal from becoming too warm, or losing water by saliva spreading, or having to slacken the pace of its activities. In the day, even though the set-point is lowered, it may be preferable to meet the set-point through behavioral means rather than disrupting sleep with bouts of shivering or other ways of heat production.

The difficulties for the set-point interpretation would be much more severe if it could be shown that hypothalamic cooling during the night led to increased heat production by autonomic means while the rat persisted in going to a cool area. To prove antagonism between behavioral and autonomic defenses over the cycle, it would be necessary to show that the ambient temperature selected in the day is so warm that it brings autonomic heat loss effectors into action. In fact, when the rats were in a thermal gradient apparatus, in the day the warmest places selected seldom exceeded 23°C; this is well below the top of their thermoneutral range. In another experiment the rat had a choice only between a 22.5–26°C environment and a 34.0°C environment (Briese, 1985). In the day it did choose the hot area more often than in the night, but it left this (presumably to cool off) at hypothalamic temperatures well below the nighttime levels; this can be interpreted as defense of a lowered set-point during the day.

In pigeons also, the use of behavioral defenses varies over the diurnal cycle. At the onset of night, more time is spent in a warm area, or working for a 1-minute influx of warm air. However, cycles of body temperature under these conditions are essentially the same as when the animals are without access to heat reinforcement. The means chosen to meet the set-point evidently change according to the availability of opportunities for behavioral thermoregulation (Schmidt et al., 1978).

In ectotherms the situation is more straightforward. The findings of Regal (1967) that lizards select cooler places to be in at night have been extended to a number of fish (e.g., Reynolds and Casterlin, 1979). The daily patterns of temperature selection may themselves be modified on a seasonal basis. In the fall, European green lizards, *Lacerta viridis*, stay in cool places for longer portions of each day until eventually they stop moving into warm places altogether (Rismiller and Heldmaier, 1982). These seasonal changes are probably a reaction to changes in daylength but might also have an endogenous component.

## CIRCADIAN RHEOSTASIS IN GENERAL

Numerous variables in addition to temperature change on a circadian basis. In fact, nowadays it is noteworthy to find a physiological variable that does not have an endogenous rhythm (Moore-Ede et al., 1982). Many instances of circadian rheostasis might therefore be expected. It is beyond the scope of this work to discuss all the possibilities. Instead some general points will be made and a few examples given.

A common way of demonstrating that a variable is defended is to force it to change to a different value and then, after the manipulation has ended, watch for its return to the initial value. In the case of a rheostatically defended variable, it is expected that the value returns not to the premanipulation level but

to a level appropriate to the postmanipulation stage of the program (e.g., Fig. 4–2). This type of experimental design is formally similar to that used in rhythms research for demonstrating the existence of some underlying oscillator as opposed to the generation of rhythms from feedback coming from successive states of the measured variable, the hands of the clock. For instance, attaching weights to plants prevents rhythmic leaf movements (Bünning, 1973); giving rats electroshock eliminates cycles of running activity for a few days (Richter, 1965). When these manipulations end the systems reattain states appropriate to the phase of oscillators that continued to run intact throughout. Rhythmic changes, then, are by no means incompatible with maintenance of regulation: the same type of experiment can be used to illustrate and illuminate both processes.

Circadian cycles are sometimes small in amplitude. Together with their rapid frequency, this may limit the types of manipulations that can be used to study regulation at particular phases of the cycle. However, a few examples are offered in support of the contention that circadian, or at least diurnal, rheostasis is widespread.

## CIRCADIAN CHANGES IN GLUCOCORTICOID FEEDBACK

Glucocorticoid levels exhibit pronounced circadian cycles. Manipulations of the negative feedback system at different phases of these cycles produce different effects. For instance, RU 486, a synthetic steroid that antagonizes glucocorticoids by binding to their receptors without having an agonist action itself, exaggerates the morning rise in ACTH in man but has little effect in the afternoon or evening, when ACTH levels are naturally low (Gaillard et al., 1984). Perhaps the system is so sensitive in the evening that even minimal amounts of glucocorticoids are sufficient to inhibit ACTH production. It has been known for some years that the effectiveness of glucocorticoids such as dexamethasone in inhibiting ACTH secretion varies with the time of day (Nichols et al., 1965). In adrenalectomized rats given replacement corticosterone in pellets releasing this hormone at a constant rate throughout the day, ACTH levels are higher in the evening than in the morning, which shows that the suppressive effect of the same amount of corticosterone is greater in the morning, the time when corticosterone levels are naturally low in rats, nocturnal animals (Akana et al., 1986). These and other studies are consistent with there being diurnal changes in sensitivity to steroid feedback.

This case of rheostasis is of particular interest because while operationally the set-point changes, the underlying mechanisms may be quite complex, depending on changes in the relative importance of hypothalamic and pituitary feedback loops. In their work with rats, Akana et al. (1986) also showed that pituitary responsiveness to corticotropin-releasing hormone (CRH) did not change between the morning and evening. They also tested the CNS-mediated response to stress: effectiveness of histamine injections in elevating ACTH was fairly similar in the morning and in the evening. Akana et al. (1986) argue that, because the ACTH response to stress was similar at different times of day, the

feedback of corticosteroids secreted cannot be very different; if it were different, the response to stress would be damped down at the time of maximal feedback sensitivity. Instead, they suggest that in the morning, when ACTH is low in rats, the CNS is not driving the pituitary to produce ACTH. The important feedback in the morning is primarily at the pituitary level. In the evening the hypothalamic drive to the pituitary is switched on, stimulating ACTH production. It is then that feedback on the hypothalamus becomes important, but because the hypothalamus is not as sensitive as the pituitary (differences in receptor affinities), this drive to the pituitary is not suppressed by feedback from the high plasma glucocorticoids in the evening. At both times, however, the drive to the pituitary from the CNS can be activated—or further activated—by stress.

Further experiments are needed before these ideas can be accepted. As Akana et al. recognize, there may be diurnal changes in the metabolism or circulation that make a given dose of histamine more effective at certain times of day. And there is no reason, in the context of the numerous other cases of rheostasis, to agree with these authors that there is anything unlikely in there being sensitivity changes to corticosterone feedback at the hypothalamic level. However, neither is there reason to reject their alternative explanation. Whether correct or not, their proposal nicely illustrates how rheostasis can be achieved by different means: instead of altering sensitivity of a single feedback site, there could be switches between two feedback sites of different sensitivities.

## INSENSITIVITY TO GLUCOCORTICOID FEEDBACK IN DYING MARSUPIALS

In a number of dasyurid marsupials (*Antechinus* spp.), there is a spectacular and synchronized die-off of the males at the end of the mating season. In nature the males usually live less than a year, with a maximum life span of 11.5 months. In captivity they can attain ages of 18 months, but this is only if they are housed singly. When kept together in groups the males are intensely aggressive and die sooner (Lee and McDonald, 1985).

Physiologically, the few weeks of mating and die-off are characterized by levels of glucocorticoids twice as high as those during the earlier stages of the life cycle. These high levels lead to suppression of the immune system and gastrointestinal ulcers; the final causes of death are opportunistic infections and hemorrhages. The high levels of adrenal steroids stem from a change in the sensitivity to feedback. Prior to the mating period dexamethasone suppresses corticosteroids, but during the mating season this suppression fails (McDonald et al., 1986). Because only small doses of dexamethasone were given (I.R. McDonald, 1987, personal communication), it is not possible to tell whether the feedback system is inoperative or whether it is less sensitive but could still be activated by higher doses.

In either case McDonald et al. (1986) call this a failure of the glucocorticoid feedback, yet from a biological point of view they do not consider it a failure (Lee and McDonald, 1985). If breeding takes place only at one time of year

(July–August) and a short life span precludes a second chance to breed, no advantage is to be gained from restraining reproductive activity in the interests of maintaining body weight and nutritional health. Instead, the males go into a breeding frenzy. Intense aggression against other males, mating with different females, and remaining mounted on the females for many hours on end contribute toward reproductive success but leave little time for feeding. The high levels of glucocorticoids presumably help provide energy for these priorities by stimulating gluconeogenesis and protein catabolism (Lee and Cockburn, 1985). Perhaps they also support the behavioral activities.

Similar channeling of energy into reproductive effort, accompanied by adrenal hyperactivity, occurs in spawning salmon (Robertson and Wexler, 1960). Examples such as these make one think differently about Bernard's statement that "all the vital mechanisms, however varied they may be, have but one end, that of preserving constancy in the internal environment".

## SUMMARY

This chapter has described numerous examples of programmed rheostasis. These concern fat and mineral storage, thermoregulation, and levels of gonadal and adrenal hormones. Many of these examples represent changes that occur during cycles—daily, estrous, or seasonal cycles. Others, like those at puberty, occur at particular developmental stages.

Two disclaimers are necessary:

1. It is not asserted, or even intended, that the examples presented here are exhaustive.
2. The authors of many of the papers describing these findings have themselves already interpreted their results in terms of set-point changes. Evidently many people have already found this a useful concept. This chapter has merely collated this material and placed it in a wider context.

The main points that emerge from collating these examples are as follows:

a. Rheostasis often arises in situations of potential conflict between the demands of different regulatory systems.
b. It is often possible to perceive survival value in changes formerly regarded as failures of homeostasis in stressful situations.
c. Adjustment of regulated levels is a common occurrence in the animal kingdom. It is not necessarily forced upon the animal by its immediate predicament but is often built into developmental or cyclical programs by evolutionary pressures.

## PREVIEW

The next chapter supports the view that rheostasis is common and valuable by providing examples of alterations in regulated levels that occur in direct reaction to unpredictable events.

# 5

# Reactive Rheostasis

## FEVER

Fever is a classic example of reactive rheostasis: the higher temperature levels are defended. In people, shivering and huddling under the bedclothes are common examples of this defense. Further evidence that set-points are elevated comes from changes in hedonic ratings: thermal stimuli that normally are rated as unpleasantly hot become pleasant during fever (Cabanac, 1969, 1971). Preferred skin temperatures are a linear function of internal temperatures, but in fever there is a shift of this relationship to higher temperatures. Shifts in threshold rather than decreased responsiveness to thermal stimuli are the main reason for the higher defended levels during fever (Cabanac and Massonnet, 1974). The correction of thermal loads produced by infusing rabbits with hot or cold isotonic saline is equally effective in the febrile and the normal state (Cranston et al., 1976).

Defense of higher temperatures is particularly clear in ectotherms, animals that must obtain their heat from external sources to keep warm. For example, desert iguanas, *Dipsosaurus dorsalis,* given access to heat lamps normally move around in such a way as to keep their body temperatures close to 38°C. Following injections of a pathogen, they spend more time under the lamps and their body temperatures rise to around 41°C (Kluger, 1979). These levels can be achieved only through the behavior of the animal. The lizard does not passively submit to fever: it actively changes its behavior to become febrile.

Thermoregulation in lizards is not radically different from that in mammals. Not only can both develop fever, but lizards will do so in response to endogenous pyrogens extracted from rabbits after they have been infected (Bernheim and Kluger, 1977). Salicylates lower fever in lizards as in mammals (Bernheim and Kluger, 1976). Finally, the preoptic area in lizards (*Tilaqua scincoides*) contains temperature-sensitive neurones (Cabanac et al., 1967), and local heating or cooling of this region instigates thermoregulatory responses (Myhre and Hammel, 1969), as it does in mammals. The main difference between ectotherms and endotherms is in the effector systems at their disposal.

The ectotherms lack physiological defenses; they have to rely on behavior to keep themselves at the regulated temperature.

This constraint makes animals such as lizards a useful preparation for studying the adaptive value of fever, because fever can be eliminated simply by depriving them of external heat sources. Kluger et al. (1975) have demonstrated that when infected lizards are prevented in this way from developing a fever, then mortality is increased (Fig. 5–1). Similar results have been obtained with fish (Covert and Reynolds, 1977). In lizards it has also been shown that bringing down the fever with salicylates increases mortality (Fig. 5–2).

The adaptive value of fever has also been measured in units that should please investigators who are interested in the validation of functional arguments: the number of eggs laid. In this case the subjects were a nondiapausing strain of grasshopper (*Melanoplus sanguinipes*). Some were fed lettuce contaminated with a pathogenic protozoan (Boorstein and Ewald, 1987). When kept at 34°C (the temperature that healthy grasshoppers of this strain prefer), the infected animals laid fewer eggs than uninfected controls. When kept at 40°C (the temperature that infected grasshoppers select), the difference between infected and control insects was greatly reduced.

What of fever in mammals? Despite the case that thermoregulation and fever are conservative in evolution and similar in different types of vertebrates and invertebrates, some people remain uncomfortable about extrapolating to man from lizards—let alone from grasshoppers! They prefer to be sure of avoiding an error of commission (erroneous extrapolation) than to risk making an error of omission (failure to extrapolate when there is in fact similarity). Testing for the function of fever is harder in endotherms. It is difficult to prevent fever without stressful external cooling or using drugs with side effects. However, some newborn mammals are more like ectotherms in that their physiological effectors have not yet developed. Newborn mice removed from their mothers soon become hypothermic. At this stage they are highly susceptible to infection; injection of a virulent virus is frequently fatal. Around day 6–9 of life mice begin to be able to maintain their body temperature at high levels. It is just at

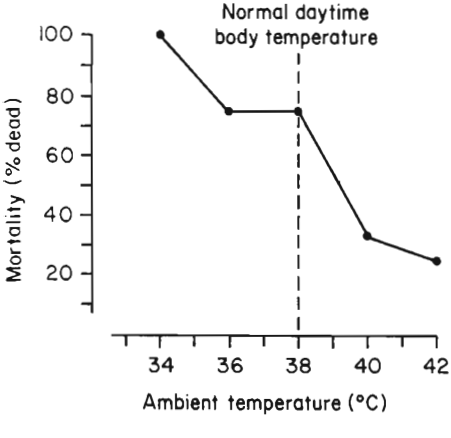



**Figure 5–1.** Mortality (% dead after 7 days) of desert iguanas injected with *Aeromonas hydrophila* and kept at different temperatures (data from Kluger et al., 1975).

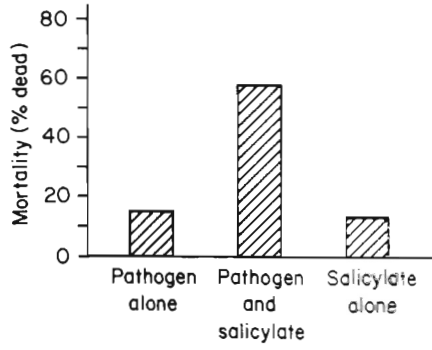



**Figure 5–2.** Effect of salicylate on mortality (% dead after 7 days) of desert iguanas injected with *A. hydrophila* and allowed to move around in a thermal gradient. The antipyretic action of salicylate was not evident in some of the pathogen-injected lizards; if these animals are excluded, then the deleterious effect of salicylate becomes more pronounced (data from Bernheim and Kluger, 1976).

the time when this independent thermoregulatory ability develops that resistance to infection increases dramatically (Teisner and Haahr, 1974). Newborn puppies with canine herpes virus survive better if they are kept warm enough to raise their temperatures to 39°C than if body temperatures remain at 37°C (Carmichael et al., 1969). With such findings in mind, it has been suggested that hyperthermia be used therapeutically in premature human infants when viral infections are suspected (Haahr and Mogensen, 1977).

Some cautions must be made. No one is advocating that fevers be allowed to rage unrestrained to dangerously high levels. As Kluger (1986) has said, "It is important to emphasize that although fever probably evolved as an adaptive host-defense response, not all fevers *must* be beneficial. In terms of evolution, a trait merely needs to have survival value in order to have evolved and been retained. This simply means . . . that statistically fever is beneficial. In individual cases, fever may be maladaptive." One may question the value of antipyretics in moderate fevers without decrying their use in extreme cases. Nevertheless, debate about the adaptive value of fever continues (Blatteis, 1986). But to talk of "non-thermal effects of fever," as Banet (1983) does, is confusing. Endogenous pyrogens, released by the macrophage-T cell complex in response to pathogens may have nonthermal effects in addition to their thermal ones. Fever is by definition a thermal matter. The empirical questions are whether high temperatures have direct effects on the invading pathogens, and whether they enhance other defenses. To the extent that they do, fever can be said to be beneficial. The overall problem though, as Banet (1983) has pointed out, is that the host has several defenses; fever may stimulate some but not others. Probably debate will continue until these various mechanisms and their interrelationships are better understood. Kluger and Rothenburg (1979) have focused on the decline in serum iron during fever. They found that bacteria in an iron-deficient medium grew fairly well at normal temperatures but not at febrile temperatures. Others have concentrated on the macrophages (monocytes). Duff and Durum (1982) have shown that interleukin-1 stimulates the proliferation of T cells in vitro better at febrile temperatures. Interleukin-1 is also part of the chain of events (pathogen → macrophage–T cell complex → interleukin-1 → CNS) that results in elevated temperatures. Fever and the response of the immune system are related not only mechanistically but also functionally, be-

cause fever enhances the production of T cells. Duff and Durum (1982) suggest that, should these phenomena occur also in vivo, fever may have a function in host defense. Similar considerations apply to the enhancing effects of febrile temperatures on the actions of interferon and on the migration of neutrophils (see Kluger, 1986).

While the problem of fever in mammals occupies the clinical limelight, the demonstrations of fever and its adaptive value remain the clearest scientifically in lizards and some other ectotherms (for exceptions, see Chapter 7). Thermal constancy is abandoned in the short term to tackle a more serious kind of inconstancy, the invasion by foreign bodies. Although fever results in further changes to the internal milieu it is, paradoxically, a weapon in the body's fight for stability.

## CRYEXIA

Newborn mice (*Mus musculus*) move around in a temperature gradient until they reach areas close to 35°C, where they stay. Mice of the same age (1–11 days) injected with bacteria or bacterial endotoxin select cooler regions, near 32°C. Lagerspetz and Väätäinen (1987), who discovered this phenomenon, call it cryexia to contrast it with pyrexia. This cryexia is regulated: if one accepts change in behavioral thermoregulation in ectotherms as evidence of a change in set-point, then one must accept similar evidence for newborn mice, which are also deficient in physiological thermoregulation. In these experiments the infected mice were initially placed at their normal preferred temperature, 35°C; they actively moved about until they reached a cooler spot. It was not that they started in a cool area and were too sick to move out.

Lagerspetz and Väätäinen (1987) also showed that pathogen-injected infant mice kept at 35°C did not survive as long as those kept at 32°C. Possibly, they suggest, multiplication of bacteria is suppressed at low temperatures as well as at high ones, and for a small animal with an already high metabolic rate, cryexia might be a better defense than the energetically more expensive fever. Subnormal temperatures have, however, also been noted occasionally in infected human infants (Epstein et al., 1951).

Temperatures that are too low may be detrimental. Mice, 1–3 days old, kept in a room at 22°–24°C had higher mortality when infected with a virus than those kept at 34°C (Teisner and Haahr, 1974). Unfortunately, the body temperature of the infected mice in the 22°–24°C room was not reported.

## INFECTION-INDUCED ANOREXIA

Infection is often accompanied by loss of appetite, as well as by fever. Such anorexia might be adaptive, a part of host defense. This idea has been developed by Murray et al. (1978). Starting with the old adage "feed a cold and starve a fever," they argued that it would be surprising if anorexia was merely an annoying by-product of infection. The matter is amenable to analysis, using experimental designs analogous to those of Kluger with fever, but with force

feeding substituted for prevention of fever. In one such experiment, mice were injected with virulent bacteria. Mortality was increased by force feeding the animals amounts that brought their total food intake up to normal. Mice allowed to express their anorexia did better (Fig. 5–3).

A different approach is to first deprive the animals and then give the pathogen. In some circumstances at least, resistance is increased. For instance, mice survive injections of *Listeria monocytogenes* after being without food for 48 or 72 hours better than fed mice. Macrophage activity is enhanced (Wing and Young, 1980). The relevance of this experimental design to infection-induced anorexia depends on the assumption that the critical aspects of this state can be mimicked by food deprivation. It may, therefore, be preferable to concentrate on comparisons between force-fed and anorexic animals, using different species and different pathogens. Even if it were determined that anorexia is widely beneficial in combating infection, that would not show that rheostasis is involved. Loss of appetite might arise in some other way. However, lowering of the set-point for body fat is one way of decreasing intake without leaving the animal hungry and motivated to search for food. It would be interesting to find out if negative alliesthesia for sweet tastes were particularly pronounced when people became sick.

Another obvious qualification is that a defense mechanism, if overused, may become a liability (Murray et al., 1978). Chronic loss of appetite contributes to cachexia and general weakness. Clinicians will have these considerations in mind. They may also wish to entertain the possibility that in the early stages of infection anorexia might be adaptive, a "sentinel of host defense" to use the Murrays' phrase.

There are numerous proposals of how such a defense might work (Murray et al., 1978). Depriving the invaders of specific nutrients is one possibility. Iron is required by bacteria, and eating might counteract the hypoferremia that occurs during infection (Tocco et al., 1983). The macrophages may also be important; they produce a factor, cachectin (tumor necrosis factor), that inhibits lipogenic enzymes in adipocytes and promotes lipolysis (Torti et al., 1985). The relationship of this phenomenon to the anorexia requires elucidation. It is not

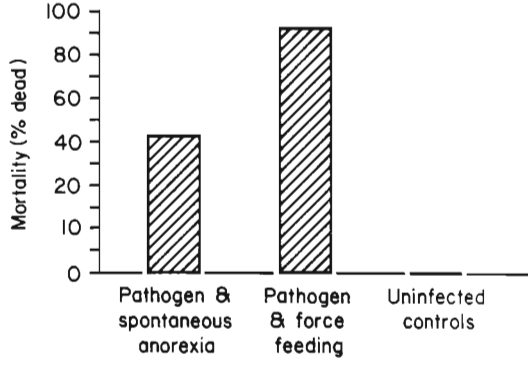



**Figure 5–3.** Mortality of mice injected with an $LD_{50}$ dose of *Listeria monocytogenes*. Left: mice given the pathogen and allowed to become anorexic. Food intake of these animals was 42% lower (day 3) and body weight fell 19% (at time of death). They were intubated without force feeding. Middle: mice intubated and force fed amounts to bring their intakes up to the level of uninfected controls. Right: uninfected controls intubated without force feeding (data from Murray and Murray, 1979).

clear whether anorexia follows from the provision of nutrients by the fat depots, or whether mobilization of lipids occurs to compensate for or anticipate decreased food intake. One way or another, the macrophages are involved in alterations of energy balance during infection. It would be remarkable if one action of the macrophages, the stimulation of interleukin-1 resulting in fever and T cell proliferation, were adaptive while another, the production of cachectin resulting in lipolysis, were deleterious. More likely both are part of an integrated host defense that might also include behavioral changes such as increased sleep and lethargy (Hart, 1987).

If it is a basic necessity, or at least highly desirable that an infected animal not eat—as a means of starving the pathogen of iron, or because it may be too sick to search for food, or whatever the reasons—then deeper interrelationships may arise between the systems that regulate body temperature and those that regulate nutrient reserves. A hint of this lies in the reduced febrile response in states of calorie-protein malnutrition (Hoffman-Goetz and Kluger, 1979). Attenuated febrile responses in starved animals have been seen in a number of experiments (review in Shido et al., 1989). In rats, the effect does not stem simply from lack of necessary substrates for thermogenesis, because heat production can be boosted by increasing the dose of the bacterial endotoxin. But it should not be assumed that food deprivation acts directly on the thermoregulatory set-point. It may attenuate fever by modifying the transduction of signals from systemically circulating pyrogens into a stimulus to the thermoregulatory systems within the CNS (Shido et al., 1989). Decreased production of interleukin-1 or other endogenous pyrogens by the monocytes may also be involved (Kauffman et al., 1986).

From an adaptive point of view, a lower febrile response in undernourished animals is understandable. As will be elaborated later in this chapter, deprivation often leads to a fall in body temperature. Hypothermia is viewed as an adjustment toward saving energy in the ever-present choice between putting energy into reserves or into maintaining high body temperatures. This presents itself in its starkest form when a severely malnourished animal needs to run a fever to combat infection. It may come down to a choice of deaths: incur the metabolic costs of the fever and fight off the pathogen but die of starvation, or preserve the last essential energy substrates but die of infection. Mortality rates associated with pathogens are indeed higher in malnourished animals (Hoffman-Goetz and Kluger, 1979). In this predicament it seems that the two systems work out some precarious not always successful compromise, setting a middle course between the Scylla and Charybdis of starvation and infection. There is still some febrile response but it is attenuated.

An important question then arises about what aspect of malnourishment initiates this attenuation. Is it a deficiency of some particular nutrient, or of protein, or of fat, or a combination of deficiencies? Is it the absolute level of some reserve, or is it the development of discrepancies between the actual and defended levels of weight? Suppose it were the latter, then there would be a reason why reactions to pathogens should include a lowering of body weight set-points. If, for whatever reasons, the animal did not or could not eat, as has

been assumed, then unless weight set-points were lowered, discrepancies between set and actual weights would develop and the febrile response might be too greatly compromised.

These are speculative thoughts, but they are not without predictive power. For instance, if this web of interrelationships is correctly depicted, then obese people who are dieting and have lost weight but are still relatively fat should have an attenuated febrile response. Hibernators at different phases of their regulated weight cycles should have similar febrile responses despite large differences in the state of their fat depots.

The present section is no more than a plea for open-mindedness and research on a problem that has received little attention. Infection-induced anorexia might just be another example of the wisdom of the body.

## THE FEVER OF STRESS

When young boxers are examined just after weighing-in before a competition fight, they commonly have temperatures 0.5°C higher than before routine training sessions at the same time and place. They do not report feeling hot, however (Renbourn, 1960). When rats are placed in a strange brightly lit area, their temperatures rise 1°C in 30 minutes, even though they spend most of the time huddled in a corner. These are examples of psychogenic hyperthermia, and they are probably regulated as is fever. At least, as with fever, administration of antipyretic drugs (prostaglandin blockers) attenuates these hyperthermias, suggesting that stress-induced elevations of body temperature also involve an upward shift in set-point (Kluger et al., 1987). The survival value of higher temperatures might be to enhance muscular activity, in rats as in athletes. The psychogenic contribution to such warming up may be to shift the thermoregulatory set-point. There may be other mechanisms involved also: in the experiments with rats, the antipyretics reduced but did not abolish the stress-induced hyperthermia.

## INJURY, HYPOTHERMIA, AND SURVIVAL

A different form of stress is that occurring after burns or after circulation to a limb is interrupted. When the circulation is restored in small mammals in an environment below thermoneutrality, there is a marked fall in heat production and core temperature. It is still possible to elicit increased oxygen consumption and shivering in the cold, but the thresholds for these thermogenic responses are lower than usual. The slopes relating the intensity of heat production to temperature remain normal despite the lower threshold, so the animals behave as if the set-point is lowered (Stoner, 1971). Thresholds for shivering in response to local cooling of the preoptic area are also lowered; in some animals, even though this area was cooled to close to 30°C, no shivering was seen. In other animals shivering could be obtained at 31°C, that is about 4°C lower than in uninjured controls (Stoner, 1972). Thresholds for shivering and nonshivering

thermogenic responses did not always move in unison (Stoner, 1972). Different circuitry or thresholds for different thermal effectors is now considered to be part of the normal complexity of thermoregulation, even in intact animals (Satinoff, 1978). The main finding is that temperature falls in the injured animal, yet effectors can still be activated. This points to some lowering of the level around which the system (or part of the complex of thermoregulatory systems) is regulating.

Although it is tempting to infer set-point changes from the shifts in thresholds for shivering and for nonshivering thermogenesis (Stoner, 1974), two strong cautions against doing so must be mentioned. First, after injury it also becomes more difficult to elicit heat loss responses in rats; vasodilation in the tail in response to hypothalamic heating occurs at a higher threshold and then disappears altogether (Stoner, 1972). Unless there is some circulatory failure interfering with this effector mechanism itself, a higher threshold seems incompatible with a downward shift in set-point. Second, in injured people, there is a breakdown of the normal relationship between core temperature and the preferred temperature for the hand. Instead, there is a scattered mess of points with, if anything, higher than usual preferred temperatures rather than maintenance of the relationship with a shift of the line toward selection of lower temperatures (Little et al., 1986). Therefore, if injury does lower the set-point, this must be accompanied by other effects.

Shock responses to injury are sometimes considered part of a disease process, but there is an alternative view (Stoner, 1961). If an animal is injured and unable to forage, then hypothermia may be beneficial. In fact food-deprived rats lose less weight in a state of shock than when uninjured (Stoner, 1961). Also raising air temperatures (i.e., preventing body temperature from falling as fast) after limb ischemia reduces survival times (Fig. 5–4). Therefore shock—at least in its thermal aspects in rats—can be viewed as a defense mechanism, as can fever.

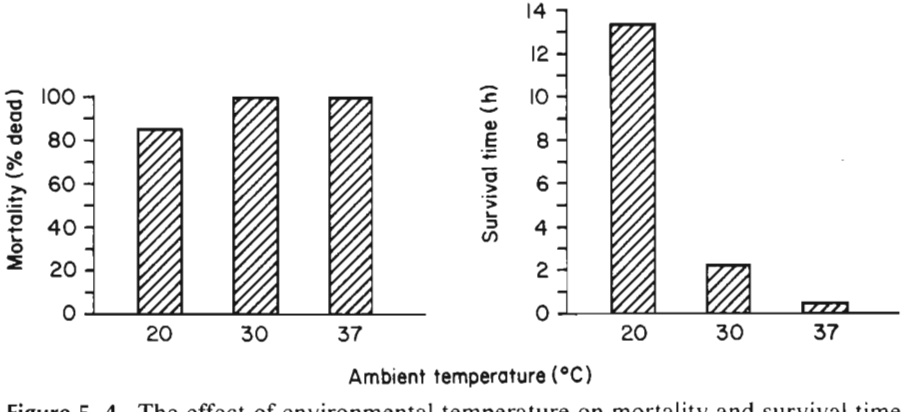



**Figure 5–4.** The effect of environmental temperature on mortality and survival time of rats after a 4-hour hind limb ischemia (data from Stoner, 1961).

Like other defense mechanisms, shock has both positive and negative aspects. Sometimes cardiovascular and metabolic complications are too great and the animal dies.

## PARAPLEGIA: PARTIAL POIKILOTHERMIA

Spinal cord transection is another type of injury in which the thermal changes that occur may not be altogether pathological. Paraplegics have lower core temperatures than control subjects in cool environments and higher temperatures in warm environments. This is sometimes referred to as partial poikilothermia (Attia and Engel, 1984). Not all of this variability is accountable for by the failure of peripheral vasoconstriction and vasodilation and the consequent inadequate buffering of the core from the outside environment. At least part of the change appears to stem from changes in thermal set-point. Paraplegic patients do not find higher temperatures as unpleasant as control subjects with the same skin temperatures. Even though the core is warmer in the heat than that of nondisabled people, and cooler in the cold, paraplegics do not experience more discomfort. These and other aspects of alliesthesia suggest that their set-point varies with the ambient temperature (Attia and Engel, 1983). The idea that one of the stimuli capable of altering temperature set-point is the ambient temperature itself has already been raised in the discussion of thermoregulation during hibernation (Chapter 4).

Attia and Engel (1984) point out that the ability of paraplegics to adjust set-point is not present immediately after injury but takes a few months to develop. They argue that it is a "purposeful, precontrived and beneficial" adaptation acting to minimize strain on the thermoregulatory system. With subjective discomfort similar, despite greater changes in body temperature than in nondisabled subjects, paraplegics will not fight harder to maintain stability, and therefore will not overtax their defenses when ambient temperature changes.

## HYPOTHALAMIC THERMAL SET-POINT AND SKIN TEMPERATURE

In dogs, temperature thresholds for the initiation of metabolic responses to cooling the hypothalamus shift to lower values when their skin is hot and to higher values when it is cold (Fig. 5–5). Similar shifts take place in the threshold for evaporative cooling in response to hypothalamic warming (Hellstrøm and Hammel, 1967; Hammel, 1970). The proportionality constants for these heat-producing and heat-dissipating responses remain virtually unchanged. In pigeons also, skin temperatures determine the thresholds for heat production (in this case in response to spinal cord cooling rather than to hypothalamic cooling) but do not alter the proportionality constants (Rautenberg, 1983).

In a cold environment the skin cools before the core. Raising the set-point on encountering cold creates a discrepancy between the set temperature and

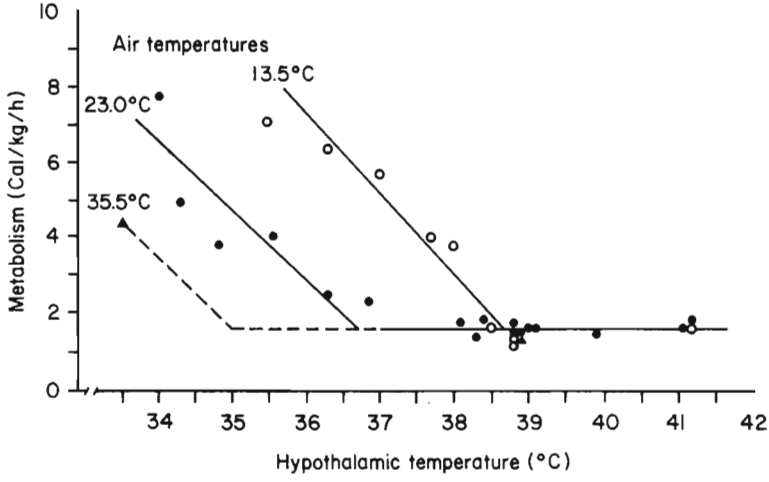



**Figure 5–5.** Heat production in a dog as a function of hypothalamic temperature at three different levels of air temperature. Metabolic rates are for 2-minute periods at the peak of responses when the hypothalamus was locally cooled (adapted from Hammel et al., 1963).

the actual hypothalamic temperature, and this results in heat production. With respect to regulation of core temperature, this heat production is an anticipatory reaction to the warning signal provided by the cool skin. The mechanism of this feedforward response is a change in set-point.

Raising the regulated level in the cold and lowering it in the heat are opposite to the changes inferred to occur in paraplegics. As discussed in the preceding section, the thermal set-point in paraplegics moves in the same direction as changes in the ambient temperature.

## REPRODUCTIVE SHUT-DOWN DURING WEIGHT LOSS: FEEDING AND BREEDING

Numerous hormonal and metabolic changes occur in food-deprived animals. This is not surprising since maintenance of proper nutrient levels and energy balance is so important to continued well-being. Some of the reactions to food deprivation may involve changes in regulated levels. For example, reproduction is often suspended in severely underweight animals. Reproduction and caring for the young are liable to fail if the parents themselves are at the margins of survival. Part of the mechanism of reproductive shut-down is a downward resetting of the gonadostat in reaction to some stimulus arising from the undernutrition. The evidence for this is that in food-deprived animals estrogens have a greater suppressive effect on LH secretion. When rats were rationed to half their normal intake, the change appeared within 7 days and at less than 10% body weight loss; no steroid-independent effect of undernutrition was detected (Howland and Ibrahim, 1973). In underfed castrated bulls, testosterone injections reduce the frequency of LH pulses compared to that in castrated bulls on a higher nutritional plane (Gauthier and Couland, 1986). Again there

was no evidence for steroid-independent effects; differences between the underfed and well-fed castrated bulls developed only after they received replacement testosterone. However, in other experiments, on rats, plasma LH was higher in castrated starved animals even without replacement testosterone; increased feedback suppression of LH by testosterone in the starved animals was confirmed (Pirke and Spyra, 1981).

There are numerous other examples of decreased output of gonadal hormones or gonadal atrophy in food-deprived animals (e.g., Eskes, 1983; Lochmiller et al., 1985). The same is true for people; it is thought that a lack of protein, rather than a reduction in total calories, leads to the decline in testosterone (Hoffer et al., 1986). The response of healthy young women to deprivation is variable, but for some subjects a weight loss of 8 kg (about 14%) is enough to lower LH levels within a few weeks (Fichter and Pirke, 1984). These various instances probably also involve gonadostat resetting, although tests for feedback sensitivity have not been done.

With accumulating information on reactive rheostasis during undernutrition, we are now in a better position to appreciate the interplay between breeding and feeding in the animal's life history. In Chapter 4, on programmed rheostasis, many examples were given of animals becoming anorexic during reproduction. It was argued that this arises from incompatibilities between breeding and feeding. Lowering of body weight set-point is a way of preventing hunger from becoming so overriding that parental duties are neglected. Nevertheless, many animals will eventually abandon their young and search for food if severely undernourished. Even with human beings social bonds weaken during starvation, and appalling instances of child neglect are not infrequent; interest in sexual matters becomes minimal (Keys et al., 1950).

Incompatibility between breeding and maintaining body weight is not only behavioral. There can also be a physiological incompatibility when undernutrition resets the gonadostat; this constitutes a further reason why too great discrepancies between actual and set weight must not be allowed to develop.

Feeding and breeding are biological superpowers struggling for dominance of the animal's activities and physiological dispositions. But their shared need to make the body that sustains them successful as a whole leads to some compromises. During reproduction, feeding and weight maintenance take second place. During winter or severe resource shortage, it is the turn of reproduction to be held in abeyance. Rheostasis is among the devices that prevent hostilities from breaking out during these carefully balanced reciprocities. Set-points for body weight are lowered during the breeding season. This is often made possible by previously having shut down reproduction and concentrated on building up energy reserves. During winter, severe deprivation, or when the cost of obtaining food increases (Perrigo and Bronson, 1985), reproduction gives way to feeding and energetic considerations. Reactive rheostasis to food deprivation, the turning down of the setting for the level of reproductive hormones, is the ultimate deterrent of the powers of feeding. But without another generation there can be no victory. This is the ultimate deterrent of the powers of reproduction.

## STARVATION AND THYROID FUNCTION

Reproductive glands are not the only ones affected by food deprivation. Output of thyroid hormones ($T_3$ and $T_4$) falls greatly during starvation. For example in bulls, after 5 days on severely limited rations, plasma levels of these hormones are about halved. The level of thyroid stimulating hormone (TSH) from the pituitary also falls (Tveit and Larsen, 1983). Falling $T_3$ and $T_4$ without a compensatory increase in TSH points to a regulated decrease in circulating thyroid hormones. Work with rats suggests that this is probably mediated by hypothalamic changes rather than pituitary changes in sensitivity to feedback. When the pituitary gland of starved rats is stimulated with thyroid hormone releasing hormone (TRH), its output of TSH is just as great as in undeprived controls. Plenty of TSH remains available in the pituitary gland during deprivation but little is released (Connors et al., 1985). The word *thyroidostat* is too awkward to be enthusiastic about, but perhaps *thyrostat* would serve to draw attention to similarities with the gonadostat system. Both the gonadostat and the thyrostat are reset during starvation.

Lower levels of thyroid hormones and the resulting decreases in metabolism contribute toward stemming weight loss and promoting weight gain should food become available. Indeed, the presence of a compensatory change in metabolism, as measured by decreases of resting $O_2$ consumption relative to metabolic mass, provides a useful index of whether an individual is below its body weight set-point (Keesey and Corbett, 1984). The declines in $T_3$ and $T_4$ during food deprivation can be seen as part of the defense mechanisms of the body fat regulatory system. Rheostasis in one regulatory system is used as an effector in another regulatory system.

## WEIGHT LOSS AND REGULATION OF ADRENAL HORMONES

Sensitivity to the suppressive effects of dexamethasone on cortisol secretion is decreased after fasting. The change was seen in half of the tests following an average loss of 8 kg in healthy subjects (Fichter and Pirke, 1986). There is a possibility that the metabolism and persistence of dexamethasone differs in the fasting state, but this was not clearly demonstrated in this study. Decreased feedback sensitivity after weight loss has implications for the interpretation of high cortisol levels in major depression and anorexia nervosa, states accompanied by weight loss (Fichter and Pirke, 1986).

## FOOD DEPRIVATION AND TEMPERATURE

Lowering body temperature when food is scarce saves energy. To the extent that lowered body temperature during deprivation depends on lowering of the regulated level, it provides another case of rheostasis in one variable being deployed as a defense mechanism for another variable. Both lowering of the thermostat and lowering of the thyrostat help maintain energy reserves.

The phenomenon is generally more pronounced in the phase of the circadian cycle when the animal is naturally inactive. For example, Inca doves (*Scardafella inca*) without food become as cool as 32°C in the night, while their daytime temperatures are close to 40°C (MacMillen and Trost, 1967). In some species of hummingbird, low temperature manifests itself as torpor, with the bill elevated and the body in a characteristic posture; torpor may be as important in compensating for periods without food as subsequent increased eating (Tooze and Gass, 1985).

It is natural to think of temperature drops in food-deprived animals as minor versions of hibernation which, as well as following seasonal programs (Chapter 4), can also occur at other times in reaction to lack of food (e.g., Fowler, 1988). The low nighttime temperature of fasting pigeons is precisely regulated (Graf et al., 1989), just as is the low temperature of mammals in deep hibernation (Chapter 4), and there are indications that thermal rheostasis is also present during shallow torpor in some other species. Although initially oxygen consumption falls progressively as it becomes cooler outside, when a certain critical level is reached metabolism increases and body temperature stabilizes. For instance, at a body temperature of 18°C, the West Indian hummingbird (*Eulampis jugularis*) increases its oxygen consumption and maintains its temperature even when the environment becomes cooler. In ambient temperatures from 18°C to normothermic levels, torpor appears to be nonregulated, with body temperatures being close to ambient levels (Hainsworth and Wolf, 1970). It could be debated whether this is a completely passive state; bearing in mind the rapidity with which thermal set-point can change, possibly the thermostat is active but its set-point is determined by the ambient temperature (cf. Chapter 4). Perhaps this is an academic distinction. The main point is that, at some level (18°C for the West Indian hummingbird), a critical temperature is reached and this is defended. The value of this critical temperature accords with the animal's habitat. For hummingbirds living in the high Andes (*Oreotrochilus estella*), the critical temperature is 6.5°C, far lower than that of the West Indian species (Carpenter, 1974).

Similar phenomena occur in mammals (see Lyman et al., 1982). Even the laboratory mouse, *Mus musculus*, can become torpid when without food; in environments below about 16°–19°C, oxygen consumption increases, and differences between body and ambient temperatures develop (Hudson and Scott, 1979). Ideally tests for regulation during torpor should include cooling and warming of thermosensitive neurones in the preoptic region. This has been done in at least one species. In the shallow torpor of deermice, *Peromyscus maniculatus* (presumably food restricted though this is not stated), at body temperatures of 17°–23°C, thermoregulation is present, with metabolic responses proportional to changes in hypothalamic temperature (Pivorun, 1986). For deprivation-induced temperature drops of only a few degrees Celsius, data are lacking to show that regulated levels are lower, though this may sometimes be inferred. For instance, despite a 2°C fall in daytime body temperature in a 22°C environment, rats still retain their metabolic responses to changes in ambient temperatures. This suggests intact thermoregulatory defenses with a lowered set-point (Markussen and Øritsland, 1986). Another example of a small

but apparently regulated decrease in body temperature during food restriction comes from work on piglets: even if they could turn on a heat lamp by making a simple operant response, their temperatures were about 0.5°C lower than when they were fed *ad libitum* (Swiergiel, 1987).

Further evidence that nutritional status (feeding) alters regulated temperatures comes from animals that thermoregulate only behaviorally. When red-eared turtles, *Chrysemys scripta,* are kept in a temperature gradient, recently fed animals spend more time in the warmer areas than those deprived of food for 3 weeks (Gatten, 1974). However, although postprandial selection of warmer temperatures exists in reptiles, some studies of this phenomenon have been methodologically defective (see Sievert, 1989, for a review).

It is usually considered that the adaptive value of such behavior is that higher temperatures after feeding assist digestion. Boa constrictors, *Constrictor constrictor,* keep under a heat lamp especially that part of their body containing recently swallowed prey (Regal, 1966). Herbivorous lizards, *Iguana iguana,* are able to extract more energy from their food when they can maintain a high body temperature for 8 hours during the day than when they can keep warm for only 4 hours (Troyer, 1987).

It might also be that lower temperatures after food deprivation help conserve energy. This was recognized by Lillywhite et al. (1973) in their studies of the western toad, *Bufo boreas*. They showed not only that starved toads selected temperatures more than 5°C lower than fed animals but also that the survival of starved toads was improved if they were kept continuously at cool temperatures or given a choice of moving into cool places (Fig. 5–6). In the case of the red-eared turtles, after fasting the average body temperature was 4.5°C lower, also enough to result in considerable metabolic savings. In box turtles, *Terrapene ornata,* the difference was only 1.5°C (Gatten, 1974).

Body temperature rheostasis in reaction to food deprivation may, of course, serve several purposes (cf. Regal, 1966). In any case, that preferred temperature alters with nutritional status is a further example of how regulated temperature can change in response to circumstances, and change rapidly: even eating a single meal worm is usually enough to make starved toads move into a warmer area within one hour (Lillywhite et al., 1973).

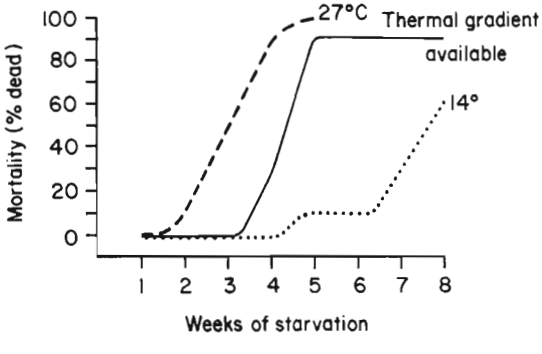



**Figure 5–6.** Mortality of western toads kept without food at different ambient temperatures. The animals in the thermal gradient could select temperatures in the 14°–35°C range (data from Lillywhite et al., 1973).

## ANOREXIA NERVOSA

It has been suggested that set-points for weight may be lowered in anorexia nervosa (e.g., Cabanac et al., 1971b). The available evidence argues against this. Efficiency of food utilization increases (Walker et al., 1979) and negative alliesthesia after eating is attenuated in anorexics. Preoccupation with food and persistent feelings of hunger are more consistent with a discrepancy between actual and set weight than with a lowering of defended weights (see Mrosovsky, 1983, 1984, for reviews).

A better candidate for rheostasis during anorexia nervosa is provided by thermoregulatory adjustments. Not only is core (sublingual) temperature often about 1°C less than normal but there is also a significant lowering (0.3°C) in the temperature for the onset of sweating (Luck and Wakeling, 1980). If defenses against higher temperatures are called into action with less provocation, then perhaps temperature is being regulated at a lower level. This would be in line with some of the previously discussed examples of hypothermia in food-deprived animals and with the suggestion that the primary event in the low body temperatures of malnourished children is a downward adjustment of the hypothalamic thermostat (Brooke, 1972). When hypothermic patients with anorexia nervosa gain weight their body temperatures return to normal values (Jonas et al., 1989).

## EXCESSIVE INTAKES: BECOMING FAT OR BECOMING HOT

Maintaining normal body temperature takes second place to body weight regulation when food is lacking but in the opposite situation of abundant palatable food, it becomes more important. At least this is one way to account for the decreased dietary-induced thermogenesis seen in warm environments. Dietary-induced thermogenesis often occurs in rats offered an array of palatable foods. Their hyperphagia is in part compensated for by dissipation of excess intake through extra heat production (review in Rothwell and Stock, 1983). At an environmental temperature of 29°C, however, less of the excess energy is dissipated as heat than at 24°C, and rates of weight gain are greater (Rothwell and Stock, 1986). Impaired defense against obesity is the cost of avoiding hyperthermia, though it should be noted that this conflict is brought on in the first place by the rat eating more than is required to maintain constant weight. Possibly the positive sensory qualities of food act as an open loop factor overriding feedback signals (see Chapter 7). This would leave the animal's set-point weight below its actual weight. A similar discrepancy arises after lateral hypothalamic lesions, which lower body weight set-points (Keesey, 1978). The increased thermogenesis after such lesions is probably mediated by a transient increase in the regulated level of body temperature (Corbett et al., 1988).

Dietary-induced thermogenesis can be demonstrated during the first few weeks of access to a palatable fatty diet. It acts as a brake on weight gain. This situation must be distinguished from that arising after prolonged feeding on

high-fat diets. In that case higher body weights may be actively defended as will be described next.

## PERSISTENT OBESITY AFTER PROLONGED FEEDING ON HIGH-FAT DIETS

If rats have access to a high-fat diet for a number of months, then they come to defend new and elevated body weights. Their obesity persists when they are returned to a chow diet. Even if their weight is brought down by restricted feeding, when given the chow diet *ad libitum* again they re-attain higher weights than animals fed on chow throughout the experiment (Rolls et al., 1980). Further evidence that higher weights are defended after prolonged feeding with high-fat diets comes from measures of energy expenditure (Corbett et al., 1986). After 6 months, energy expenditure is not excessive. Oxygen consumption indexed to metabolic mass (body weight$^{0.75}$) is the same as that of chow-fed controls. But the capability of lowering resting metabolic rate in response to a challenge remains. When the rats chronically fed the high-fat diet are food-deprived, then their oxygen consumption falls more than would be predicted purely as a result of their reduced body mass after deprivation.

After several months on a high-fat diet, the number of cells in fat depots increases (Lemonnier, 1972; Faust et al., 1978; Corbett et al., 1986). This change could explain the higher regulated level for weight. If the defense of the size of fat cells is an important factor in body weight regulation (Faust et al., 1976), then animals whose adipose tissue has become hyperplastic have more fat cells to fill up to the defended size. Because it is very difficult, perhaps impossible, to reduce the number of fat cells, the elevated set-point for body weight becomes institutionalized in this structural and possibly pathological change, even when the animal is returned to a chow diet. An analogous situation of vascular changes and persisting hypertension will be discussed later in this chapter.

## VASOMOTOR TONE: COLD VERSUS BARORECEPTORS

Constriction of peripheral arterioles reduces heat loss. It also raises blood pressure. This brings the maintenance of a steady blood pressure and a steady temperature into conflict when a cold environment is encountered. It might be thought that the matter could be resolved simply by allowing the two systems to compete only for control of vasomotor tone, while at the same time using other unshared effector mechanisms to hold temperature and pressure constant as much as possible. The actual vasomotor tone would depend on how high were the pressures and how low were the temperatures that had been reached. However, it appears that the situation is more complex.

Giving drugs that raise blood pressure (pressor drugs) to squirrel monkeys in a cool (10°C) environment reveals that interactions spread beyond the blood vessels themselves. There is a generalized inhibition of heat-producing and heat-conserving responses. The drug-induced vasoconstriction results in ele-

vated blood pressure. This in turn, via the sino-aortic baroreceptors, leads to inhibition of shivering, heart rate, and oxygen consumption, and temperature falls (Wasserstrum and Herd, 1977a). Despite the vasoconstriction produced by the drugs, there is a fall in rectal temperature. It is almost as if high blood pressure had told the animal that it was in a warm environment rather than a cool one, and that heat production should be shut down.

Support for the view that cold and pressure do not merely compete for vasomotor control comes from observations of what happens when monkeys untreated with drugs are first put in the cool environment. Not only is there vasoconstriction and elevation of blood pressure but there is also an increase in heart rate (Wasserstrum and Herd, 1977b). Presumably the latter contributes to the pressure rise of 24 mm Hg. Rectal temperatures fell by 1.6°C in these experiments. This large drop may be attributed in part to the limited options for movement and the fact that the monkeys had been trained to sit still.

Thus, the battle is not simply over particular effectors but over a variety of responses. In the conditions of this experiment, 10°C was a major challenge to thermoregulation, and temperature was not maintained. But neither was blood pressure. The baroreceptor reflex system was not turned off, however, because when pressor drugs were given, heat production was inhibited.

The question is, at what level does the interaction between temperature and pressure regulation take place. There might be competition between cold and baroreceptors for control of the sympathetic nervous system (see Wilson and Fyda, 1985). This in turn controls a variety of effectors such as heart rate and vasomotor tone. The suppression of brown fat temperature and thermogenesis after stimulation of sino-aortic baroreceptors is likely to result from decreased sympathetic activity rather than from decreased heart rate (Nagasaka et al., 1984). It is also conceivable that changes in sympathetic activity result from rheostasis: cold and high blood pressure might reciprocally alter each other's regulated levels with consequent changes in sympathetic and other outputs. At least this way of looking at things leads to testable predictions. For example, if high blood pressure lowered thermal set-points, then a monkey in a cool environment should decrease its rate of working for bursts of radiant heat when given pressor drugs. Likewise, for a person in a cold environment, the unpleasantness of a cold stimulus should be somewhat reduced if blood pressure were experimentally raised to higher levels.

Another approach is to study the relationship between blood pressure and temperature in greater detail and see what emerges. This has been done by Hohtola et al. (1980), who placed pigeons in a cool (12°C) environment and measured the inhibition of shivering produced by noradrenaline injection. The relationship between thermal and circulatory controls is presented as a trajectory on a shivering–blood pressure plane (Fig. 5–7). This treatment of the data is instructive. It suggests that two mechanisms are involved in the reduction of shivering. First, there is a rapid inhibition occurring within a few minutes when the blood pressure increases by 40–60 mm Hg. Second, a slower-acting depression manifests itself as the effects of noradrenaline on blood pressure wear off. Despite a normalization of blood pressure, the shivering remains inhibited.

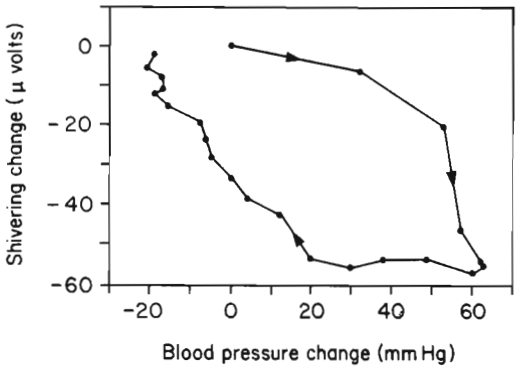



**Figure 5–7.** Changes in mean arterial pressure and shivering induced in pigeons by injections of noradrenaline. The interval between two points is 1 minute. The arrows indicate the order of these measurements, with the first point being the time of injection (adapted from Hohtola et al., 1980).

Probably the longer-lasting effect depends on some central action; intrahypothalamic injection of noradrenaline does inhibit shivering in the pigeon (Hissa and Rautenberg, 1974). Central effects could also explain the finding that noradrenaline, although it is generally a vasoconstrictor, in these experiments actually reduced the cold-induced vasoconstriction in the pigeon's feet. Whether experimental injections of noradrenaline block thermal effectors (Hissa and Rautenberg, 1974) or lower thermal set-point (Zeisberger and Brück, 1971) is a different question from whether an elevation of blood pressure, acting rapidly through sino-aortic baroreceptors, lowers thermal set-point. It is clear that in the pigeon, as in the monkey, higher blood pressure affects several aspects of thermoregulation. "Because both systems use partly the same effectors, a physiological decision making is required when thermal and circulatory challenges are opposite" (Hohtola et al., 1980).

The decision is probably taken by a "parley at the summit," in this case the preoptic region and anterior hypothalamus. Almost two-thirds of the thermosensitive neurones in this area also respond to changes in blood pressure, while only just over a third of the thermally insensitive neurones respond to pressure changes (Koga et al., 1987; Fig. 5–8). Dual sensitivity at the neuronal level is a way of mediating interactions between different homeostatic systems (see also Boulant and Silva, 1988), but the details are puzzling: the percentage of warm-sensitive neurones that are excited by low blood pressure is almost five times greater than the percentage that are inhibited (Fig. 5–8). This does not readily explain the heat loss and inhibition of shivering produced by a *rise* in pressure, as discussed above (Wasserstrum and Herd, 1977a), since activation rather than inhibition of warm-sensitive neurones leads to heat loss. The electrophysiological data are more consistent with a mechanism for inhibiting shivering after a *fall* in blood pressure, something that has also been reported (Ishii and Ishii, 1960). "Such centrally evoked hypothermia is a response having survival value which enables the organism to adapt to the reduced blood supply by lowering tissue metabolism by hypothermia" (Koga et al., 1987). There is, in fact, some evidence that hypothermia does increase survival time after hemorrhage (Tanaka et al., 1983). Perhaps, depending on the thresholds and quantitative parameters, in some circumstances the more numerous warm-

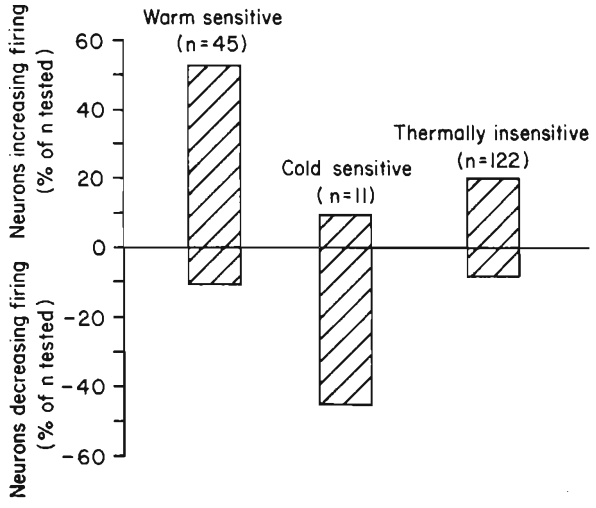



**Figure 5–8.** Percentages of neurons in different categories of thermal sensitivity that changed their firing rates in response to a fall in blood pressure. Recordings were made from neurons in the anterior hypothalamic/preoptic region of anesthetized rats (data from Koga et al., 1987).

sensitive neurones that are excited by low blood pressure are in charge while in other circumstances the less numerous warm-sensitive neurones that are inhibited by high pressure gain the upper hand. Both low and high pressure could then inhibit shivering (see also Hori et al., 1988).

## HEAT STRESS

Extensive observations on heat stroke have been made in Saudi Arabia at a body cooling unit established to assist pilgrims at Mecca making the Hadj. Comatose patients brought to the unit had hot dry skin and were not sweating even though their rectal temperatures ranged from 40.5° to 45.6°C. Some individuals were even shivering, despite core temperature as high as 41.0°C, that is about 4°C above the usual shivering threshold (Attia et al., 1983). Heat-stressed sheep display similar signs. Peripheral vasoconstriction, as well as shivering, occurs when the animals collapse and become comatose. An upward shift in set-point accounts for the elevated shivering threshold, along with the presence of shivering and vasoconstriction (Attia et al., 1983).

Raising set-point when the body is dangerously hyperthermic seems counterproductive and stupid. Perhaps it should be classified as an example of pathological rheostasis associated with a breakdown of normal functioning (Chapter 7). However, those studying the phenomenon have suggested that it may be of value as a last-ditch attempt to preserve the integrity of vital organs. During severe heat stress, circulation to the periphery increases so much in the interests of heat loss that blood supply to the brain and heart may fail. In extremis, the conflict between maintaining blood pressure and thermoregulation may tilt back in favor of the baroreceptors (Attia and Khogali, 1983; Hales, 1983).

## PHYSICAL TRAINING

Obviously it would be advantageous to avoid heat stroke in the first place if possible. Athletes at rest have slightly lower body temperatures than unfit people. Physical training, or even passive exposure to heat for an hour a day over a few days, lowers thresholds for both sweating and shivering (Hessemer et al., 1986). This shift in set-point may provide a wider safety margin between the regulated temperature and that at which heat exhaustion occurs (Olschewski and Brück, 1988).

## CHEMOSTAT RESETTING AT HIGH ALTITUDE

To obtain enough oxygen at high altitudes it is necessary to increase ventilation. However, a conflict arises because increased ventilation reduces $P_{CO_2}$ and produces respiratory alkalosis. There may be some advantages of respiratory alkalosis. The increased affinity of oxygen for hemoglobin when pH is high may assist in loading the blood with oxygen at high altitudes (West, 1989). Nevertheless, respiratory alkalosis inhibits breathing and oxygen intake. This conflict is eventually resolved by a downward shift in the threshold for the ventilatory responses to $CO_2$ to values close to 30 mm Hg. This shift does not occur at once. Initially, before the shift in threshold to $CO_2$, respiratory alkalosis puts a brake on increased ventilation. Suboptimal oxygenation and fatigue may still be present. After a few days at high altitude, the shift in chemostat threshold permits yet greater ventilation and oxygenation. After people have been at high altitudes for a few days their ventilation is even greater than that obtained immediately after exposure to equivalently low oxygen tensions at sea level. Increased ventilation continues for a number of days after descent to low altitudes (Severinghaus et al., 1963).

If the threshold shift is adaptive, why does it take so long to occur? After all, $CO_2$ chemostat thresholds can shift rapidly during sleep (Chapter 4). The answer may be that there has been insufficient evolutionary pressure for a rapid response to hypoxia. "Modern transportation and the availability of high-altitude chambers that allow truly rapid ascent may have uncovered an evolutionary loophole not encountered by primitive humans who could only ascend slowly and thus did not need to cope with the problem. This dilemma reflects the vastly different time constants for the ventilatory response to hypoxia (seconds to minutes) and the renal compensatory responses to respiratory alkalosis (days to weeks). Initially the problem is resolved by a compromise—a ventilatory increase that falls considerably short of full expression, with suboptimal maintenance of oxygenation but also an acid-base disturbance that is considerably less severe than might occur with a full ventilatory response to hypoxia" (Weil, 1986).

The turning down of the chemostat setting at high altitudes starts with a reaction to lower oxygen pressures. This reactive rheostasis does not substitute for the programmed chemostat resetting during pregnancy (Chapter 4). Acting together the two effects can greatly reduce alveolar $CO_2$ pressures. In a sample

of pregnant women living at 4,400 m in the high Andes, $P_{CO_2}$ averaged only 23 mm Hg (Hellegers et al., 1959), that is, almost half the value (40 mm Hg) common at sea level in non-gravid females and in men.

## THERMOREGULATION DURING HYPOXIA

Increased ventilation is not the only response to hypoxia. Another is to lower body temperature, thereby lowering the demand for oxygen. Indeed, one of the early techniques for inducing hypothermia in mammals was to enclose them in a cooled jar with limited air (Giaja and Andjus, 1949). Whether thermal set-point changes in this situation is not known. Decreased heat production may stem simply from reduced oxygen transport (Horstman and Banderet, 1977). However, when hypoxic ectotherms actively move to a cooler part of their environment (Dupré and Wood, 1988), changes in regulated level can be inferred.

## CHEMOSTAT RESETTING AND LOW SALT DIETS

Thresholds for the ventilatory response to $CO_2$ are set to higher levels in dogs fed a diet low in salt; there are no major changes in the slope of the function relating the ventilatory response to $CO_2$ levels (Anderson and Jennings, 1988). These effects are not very consistent from animal to animal and seem to depend on how long the dogs are fed the diet; the mean increase in $P_{CO_2}$ is about 4 mm Hg. The reason for shifting the threshold to $CO_2$ is probably that it helps preserve a constant pH. When excretion of sodium is low, bicarbonate levels rise. Without an increase in plasma $CO_2$ (elevated ventilatory threshold to $CO_2$), hydrogen ion concentration would be driven down (pH rise) by the increased bicarbonate. The pH, in the normothermic state, is extremely important in allowing proteins to function effectively as enzymes. Presumably, on a low-salt diet the preservation of a constant pH takes precedence over the preservation of the usual levels of $CO_2$ in the blood.

It is noteworthy that when osmolality is low as a result of lack of sodium in the diet, the $CO_2$ chemostat is set to higher levels, whereas when osmolality is low during pregnancy, as a result of a downward shift in the osmostat, the $CO_2$ chemostat is set to lower levels (Chapter 4).

## HEAT STORAGE IN ARID CLIMATES

In the desert the camel faces a conflict between spending water for sweating and saving water to maintain hydration. The large-amplitude daily temperature rhythm described in Chapter 1 is a way of economizing on water. The outlines of this phenomenon were known long before the work of Schmidt-Nielsen and his colleagues in the 1950s. As early as 1909 Cleland had taken body temperature measurements on camels. He even suggested that the oscillations of

temperature arose "as the result of a successful attempt to conserve water." Despite this insight, he wrote that "the camel resembles, to some extent, cold-blooded animals such as reptiles, inasmuch as there is a wide range of temperature, varying with external conditions, the oscillations sometimes being as much as nearly 8°F [4.5°C]." By association with reptiles, change has been interpreted as being forced upon the camel by its varying environment. It remained for Schmidt-Nielsen et al. (1957) to insist that temperature was well regulated. The evidence that thermal set-points change during the daily cycle is somewhat indirect, but compelling enough.

Various points demonstrate that body temperatures do not merely depend directly on environmental temperatures. For instance, Schmidt-Nielsen (1964) noticed on several occasions that rectal temperature fell particularly sharply at about 6:00 am. Air and radiation temperatures were already rising at this time. An increase of skin temperature at this time indicated that the camels were giving up more heat to the environment through vasodilation. The fact that the camel is capable of increasing its heat loss to the environment means that previously, in the early hours of the morning, it is not using the cooling power of the environment to the full effect. This in turn means that the nocturnal hypothermias are regulated, not passive.

The same is probably also true of the high daytime temperatures. At least the camels never allowed their body temperature to rise above 40.7°C, even during the hottest months of the Saharan summer. That evaporative cooling through sweating occurred at 40.7°C, but was not used by dehydrated camels in the 37°–40°C range, suggests that the set-point for initiating sweating had been raised.

In addition to sweating, the camel has a few other defenses against overheating at its disposal. It is too large to escape the sun's rays by burrowing into the ground, but it can take some other actions to decrease heat gain. Dehydrated camels usually sit with their legs under their bodies and swivel round during the day, exposing as small as possible a surface area to the sun. Well-hydrated camels often stretch out on hot days (Schmidt-Nielsen, 1964). Also, groups of camels reduce their exposed areas during the heat of the day by huddling tightly together (Gauthier-Pilters, 1958). Information on the body temperatures at which such behaviors occur are not available. If behavioral defenses were brought into action at only slightly elevated temperatures, and appreciably below 40.7°C, they could be taken as indicative of a deviation from a temperature set-point that remains constant, rather than of regulation around a set-point that climbs during the day. Suppose this were found to be the case. Then there would be a situation in which behavioral defenses occurred at one level and sweating at another, higher level. That would imply both that set-points are fairly constant and that they are raised. This may seem contradictory, but it is no problem if it is recalled that there may be parallel control circuits for different effector systems, each with its own set-point or threshold (Satinoff, 1978). The critical thing for the camel is that the set-point of the circuit controlling sweating be raised. There is no particular conflict between using other thermoregulatory defenses and maintaining water balance. In a dehydrated camel it might even be adaptive to have these other defenses brought into action at lower temperatures; this would postpone the time at which tem-

perature rose to levels necessitating use of evaporative cooling. Hierarchically arranged multiple systems for temperature may well be an example of evolution as a tinkerer—making use of material already on hand—rather than as an engineer (Jacob, 1977; Satinoff, 1978). But the tinkerer is creative enough to find specialized uses for separate circuitry.

Perhaps the most telling point in favor of there being changes in thermal set-points is that in the dehydrated camel not only are the daytime peaks raised—that might be accounted for by lack of sufficient water for sweating—but the nighttime troughs are also depressed (Schmidt-Nielsen et al., 1957). It is highly improbable that dehydration directly forces these troughs on the animals.

There are further experiments that should be done. Can heat production in camels be increased during the day by temporarily cooling the hypothalamus from 40° to 38°C? Does the body temperature rhythm have a large amplitude even when the animals are kept in constant conditions? On this last point there are some data for other species living in arid regions. The black-tailed prairie dog, *Cynomys ludovicianus,* has large-amplitude (e.g., 3.5°C) temperature cycles even when kept continuously at 23°C. In addition to the changes occurring anyway in constant conditions, the body temperature rises in response to high ambient temperatures. The ability to store heat in the day probably helps prairie dogs to economize on water in their natural habitat (Reinking et al., 1977).

Returning to camels, overall the simplest explanation of the available data is that temperature follows a rising and a falling set-point. Temperature rheostasis is programmed into the animal over evolution, but it is exaggerated by dehydration. There is probably a component reactive to high ambient temperatures because in the winter the cycle amplitudes are around 2°C whereas in the summer they reach as much as 6°C (Sergent and Lhéritier, 1919; Schmidt-Nielsen et al., 1957).

Probably numerous other species inhabiting arid regions react to dehydration in similar ways. Water-deprived ungulates such as Grant's gazelle, *Gazella granti,* allow their rectal temperature to become about 2°C warmer than when hydrated before they start to pant. Other species, such as zebu steer, *Bos indicus,* rely on sweating rather than panting to cool; they also show an upward shift in temperature for initiation of this response (Taylor, 1970). Although the thresholds for dehydrated animals are higher, once cooling responses have been initiated the slopes of the functions relating these responses to body temperature are sometimes fairly similar in hydrated and dehydrated animals; this is consistent with a shift in set-point (Fig. 5–9).

Ectotherms living in the desert also face conflicts between maintaining water balance and keeping cool. With this in mind, Dupré and Crawford (1986) demonstrated that injecting hypertonic saline into desert iguanas, *Dipsosaurus dorsalis,* raised their threshold for panting by several degrees Celsius. Withholding water also resulted in some lesser threshold changes, perhaps triggered by reductions in plasma volume.

In these experiments the lizards were restrained. If dehydration altered a single set-point controlling all thermal responses, it would be predicted that unrestrained lizards in a thermal gradient might actually seek out a warmer

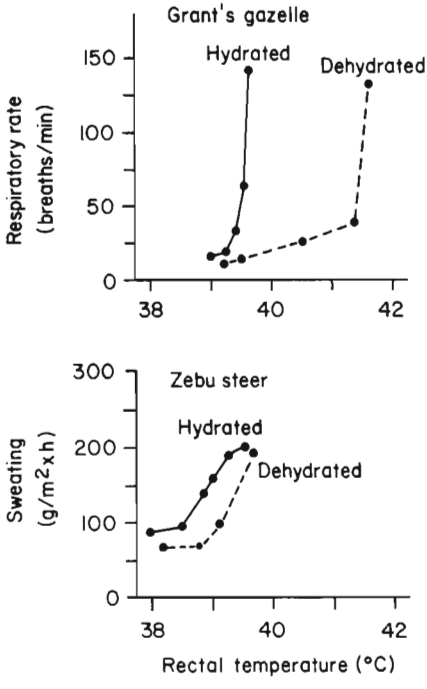



**Figure 5–9.** Heat loss responses as a function of body temperature during hydration and dehydration of two species of ungulate inhabiting arid regions in Africa. Points are means of measurements on several animals (adapted from Taylor, 1970, *Am. J. Physiol.* **219,** p. 1138).

place after receiving injections of hypertonic saline. This would be surprising because it would be adaptive for a dehydrated animal to avoid warm places. Tests of behavioral thermoregulation by desert iguanas have not provided consistent information on this point. Following injections of hyperosmotic saline solutions, these animals waited until they reached lower body temperatures than controls before leaving a cool area (i.e., had depressed lower limit temperatures) but their upper limit temperatures for leaving a warm area were affected only marginally. Moreover, injections of hypoosmotic solutions also reduced lower limit temperatures (Dupré and Crawford, 1985). The influence of water balance on thermal preferences have been demonstrated more clearly in another lizard, *Sceloporus undulatus*. Dessicated animals of this species remained buried for more time than hydrated controls, and when they were active above ground they selected lower temperatures (Crowley, 1987). Although the effects are not always straightforward, dehydration also results in selection of lower temperatures by waterproof frogs and by some other ectotherms (see Shoemaker et al., 1989).

Probably there are different thermoregulatory circuits for different effectors (Satinoff, 1978). Perhaps dehydration affects different responses in different ways. For example, in rabbits, dehydration abolishes panting but does not alter the vasomotor response to heating of the preoptic region (Turlejska-Stelmasiak, 1974). The fall in body temperature produced by warming the preoptic area is the same in both dehydrated and control animals. If there are similar situations for people, with dehydration changing one thermoregulatory response but not another, then it would be interesting to test thermal alliesthesia during water deprivation.

## HYDRATION AND THERMOREGULATION

Although conflicts between maintaining water balance and maintaining constant temperature are especially likely to arise in desert animals, species in other habitats may encounter similar problems and the mechanisms for solving them are probably similar. When people exercise, their temperature rise is greater if they become dehydrated. In the hypertonic state there is an elevated threshold temperature for the initiation of sweating. Such phenomena have been described as "a failure of temperature regulation" (Horstman and Horvath, 1972) and an "impairment of thermoregulation during dehydration" (Boulant and Silva, 1988). However, the regulatory system is operating as effectively as before. The increments in sweating per °C change in body temperature remain the same (Fig. 5–10). It is as if the thermal set-point rises during dehydration. Similar effects occur in other species (See Baker, 1984, for a review).

A mechanism for the effects of dehydration on thermoregulation probably exists at the neuronal level. In the rat, firing rates of a sizeable proportion of warm-sensitive neurones in the preoptic area are inhibited by hyperosmotic conditions; only a few are excited (Nakashima et al., 1984). In other studies with the same species, Boulant and Silva (1988) found that more warm-sensitive neurones were excited than were inhibited by hyperosmotic stimuli. Nevertheless, 11% of the warm-sensitive neurones were still inhibited. It is this population, they suggest, that controls heat-loss responses and is responsible for the increase in temperature during dehydration. The population of warm-sensitive neurones that are excited by hyperosmotic stimuli may control water intake and retention (Fig. 5–11). If this suggestion is correct, a natural question is: What is the advantage of making an osmosensitive neurone, whose job is to control water balance, also be sensitive to thermal input? Perhaps thermal sensitivity is a way of introducing feedforward into the system. Heat commonly produces dehydration. This effect could be anticipated by increased drinking and water retention, if neurones controlling such effectors were also excited by warmth. Feedforward from warmth does not necessarily have to act on the controlled variable (see Fig. 1–1); instead it might lower the set-point of the osmoregulatory system, thus reciprocating for the elevation of thermal set-point produced by hyperosmotic conditions. Whatever the merits of this speculation, it is easy to agree with the more general statement that endowing neurones with multiple sensitivities provides a basis for interactions between

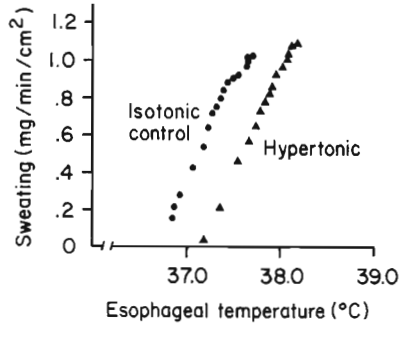



**Figure 5–10.** Sweating from the chest of a subject during exercise in the heat following infusion of hypertonic saline and during a control test. (Adapted from Nadel, 1983, Factors affecting the regulation of body temperature during exercise. *J. Thermal Biol.* **8,** p. 167. Copyright 1983, Pergamon Press, PLC.) Similar data were obtained for forearm blood flow.

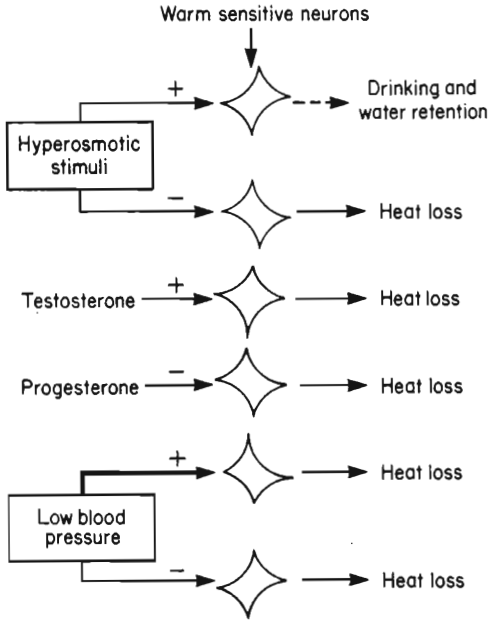



**Figure 5–11.** Multiple sensitivities of some neurons in the preoptic region of the hypothalamus, based on information in Koga et al. (1987), Tsai et al. (1988), and Boulant and Silva (1988). The diagram shows only a few of the interactions in the preoptic region between different regulatory systems. Multiple sensitivities also occur in cold-sensitive and temperature-insensitive neurons. Some warm-sensitive neurons also respond to low blood glucose (see Boulant and Silva, 1989, for a more extensive diagram). The possibility of additional overlapping sensitivities is not excluded. For example, research is needed to discover whether warm-sensitive neurons responding to testosterone also respond to progesterone. The arrows do not imply that pathways are necessarily direct; some effects might be mediated through nonspecific arousal and activation. The dotted arrow shows a speculation about the influence of warm-sensitive neurons that are excited by hyperosmotic stimuli (Boulant and Silva, 1988).

different homeostatic systems (Boulant and Silva, 1988). This applies not only to osmoregulation and thermoregulation but also to the effects of gonadal steroids on thermoregulation (e.g., during the menstrual cycle and lactation, Chapter 4) and to interactions between blood pressure regulation and thermoregulation. Electrophysiological testing for overlapping neuronal sensitivities is likely to be a fruitful line of research for anyone interested in interactions between different homeostatic systems and in rheostasis. The preoptic hypothalamus appears to be a key integrative area (Fig. 5–11).

Water loss during prolonged exercise results in both osmotic and volume change of the blood. Independent experimental manipulation of these factors shows that both hyperosmolality and hypovolemia by themselves produce a shift in thermal set-point (Harrison et al., 1978; Nadel et al., 1980), but there are some interesting differences. In the hyperosmotic state, the slope of the line relating blood flow in the forearm or sweating to temperature remains the

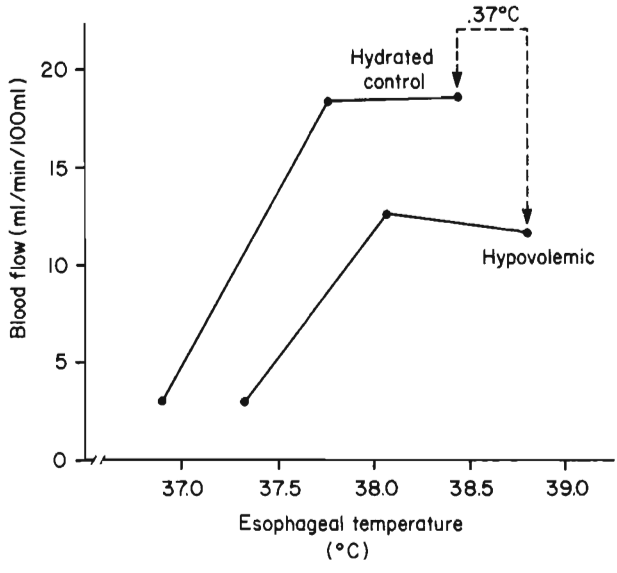



**Figure 5–12.** Forearm blood flow in a group of subjects exercising in the heat. The body temperature difference after 30 minutes was significantly different between the hydrated control condition (no pretreatment) and the hypovolemic condition (pretreatment with diuretics) (adapted from Nadel et al., 1980, *J. Appl. Physiol.* **49,** p. 718).

same. In the hypovolemic state, in addition to the threshold shift, there is a decrease in the maximum blood flow (Fig. 5–12). In these experiments blood volume was reduced by giving subjects diuretics for several days before exercise. The greater temperature rise during the early stages of exercise presumably resulted from the increased threshold for heat loss responses. The reduced maximal blood flow response might have resulted from reduced baroreceptor firing in the hypovolemic state (Nadel, 1983). As described in a previous section, temperature and pressure inputs compete for vasomotor tone. The temperature—pressure antagonism is presumably still present during dehydration. This creates the possibility for interactions between three homeostatic systems, those for temperature, pressure, and water balance (see Nadel, 1983, for elaboration).

Even though hyperosmolality or hypovolemia can in themselves shift thermal set-point, normally when dehydration occurs during exercise both volume and osmoreceptors act cooperatively. There are, however, some clinical situations in which the usual harmonious relationship between volume and osmoregulation becomes dangerously disrupted.

## SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (ADH) SECRETION: OSMOSTAT RESETTING

In this syndrome, the secretion of ADH is inappropriate because the body is in neither a hypovolemic nor a hyperosmotic state. A major component of the syndrome, not included in the title, is inappropriate drinking. Patients are sometimes desperately thirsty. The combination of the high water intake and the high water retention resulting from the ADH leads to dilution of salt and hypoosmolality. Expansion of body fluids following drinking stimulates the vol-

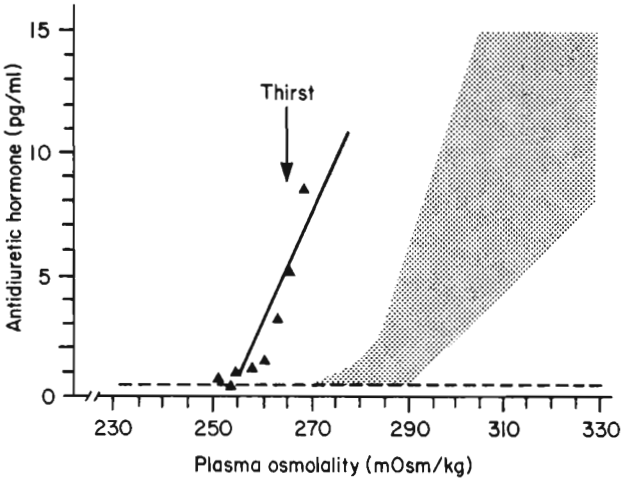



**Figure 5–13.** Resetting of the osmostat in a patient with lung cancer. Shaded area shows the normal range. Arrow shows the osmolality at which thirst was reported (adapted from Robertson, 1978).

ume receptors, which remain functional. This leads to an increased excretion of salt (Rose, 1984).

There are various subtypes of the syndrome of inappropriate ADH secretion (Robertson et al., 1982). In some, ADH output is unrelated to plasma osmolality and appears to occur at random. In others, ADH secretion remains proportional to osmolality but the threshold is lowered. Instead of ADH secretion increasing when plasma osmolality reaches a threshold of about 280 mOsmol/kg, it may start to increase at values as low as 255 mOsmol/kg (Fig. 5–13). In these cases there is a "reset osmostat" (Robertson et al., 1982). Thresholds for thirst are also lower in some cases.

Inappropriate ADH secretion occurs in a remarkably wide range of clinical situations, including drug treatment, various neuropsychiatric disorders, pulmonary diseases, and postoperatively; it may also be sustained after administration of ADH. There are no suggestions that the syndrome has beneficial aspects; indeed, there are occasional fatalities in patients with this disorder (Rose, 1984). Osmostat resetting during inappropriate ADH secretion is an example of pathological rheostasis. However, besides occurring during some types of inappropriate ADH secretion, and in the occasional case of chronic hypernatremia (elevated osmostat, e.g., Thompson et al., 1987), osmostat resetting also occurs in circumstances where it has a discernible function, as will now be described.

## OSMOSTAT RESETTING DURING HYPOVOLEMIA

Thresholds for ADH secretion shift downward in hypovolemic states. The simplest examples are those in which hypovolemia is not accompanied by osmotic changes. For instance, simply standing up increases the amount of blood in the feet and reduces central blood volume (the volume receptors are thought to be in or around the heart; Wang and Goetz, 1985). The change in posture reduces the threshold for ADH secretion by a few mOsmol/kg (Robertson and Athar,

1976). In rats, intraperitoneal injections of colloids such as polyethylene glycol have been used to produce hypovolemia without altering osmotic pressure; thresholds can be reduced by about 5 mOsmol/kg if volume reductions are sufficient. The responsiveness (slope) of ADH output to changes in osmolality also increases (Dunn et al., 1973).

Osmostat resetting in these cases is not inappropriate because hypovolemia is present. It is an adaptive compensatory response; the extra ADH enhances water retention, and this tends to restore blood volume. It serves "a legitimate albeit conflicting homeostatic purpose" (Robertson et al., 1982). This is another example of how rheostasis in one system, osmoregulation in this case, becomes an effector mechanism for another regulatory system.

ADH (vasopressin), with its powerful vasoconstrictor action, is also an effector in blood pressure regulation. High ADH after hemorrhage serves to maintain blood pressure rather than osmotic pressure (Wang and Goetz, 1985).

Osmostat resetting also occurs after water deprivation and when blood volume is expanded by injections of hypertonic saline. The effect has been found by assaying ADH directly (Robertson and Athar, 1976) and has also been inferred from steep decrements in water excretion at particular osmolalities (Moses and Miller, 1971). With manipulations such as infusing hypertonic fluids, or dehydration, osmotic as well as volume changes are present. Possibly prolonged osmotic stimulation during water deprivation, rather than hypovolemia, might be responsible for the lower ADH secretion thresholds. Whatever the case, the rheostasis serves to combat the effects of these challenges.

## LOCAL RESETTING OF TEMPERATURE: THE WOLF'S FOOT PAD

The temperature of some parts of the body can be regulated at a different level from that of the main core. An extreme example is found in the foot pad of wolves (Henshaw et al., 1972; Swan and Henshaw, 1973). Lacking fur on the soles of their feet, wolves encounter a double problem when standing on snow that may be as cold as −30°C. They have to prevent their feet from becoming frostbitten, but they also have to stem the loss of heat from the body through the feet to the substrate. A well-acclimatized adult wolf does the optimal thing: it lowers its foot temperature to close to 0°C while keeping the rest of its body close to its normothermic level (about 38°C). This prevents the tissues in the extremities from freezing yet minimizes the drain of heat. Keeping the foot pad at 15°C would also prevent frostbite, but heat loss would be much greater. Experiments on anesthetized gray wolves, *Canis lupus*, in which the foot was immersed in a subzero coolant, showed that there is active regulation of the temperature in the extremities. After dropping to near 0°C, the temperature of the foot remained remarkably constant. The tissues in the foot itself are not capable of generating enough heat to maintain themselves against a −30°C gradient. They have to rely on the warmth of blood coming from the core. Now in the experiments on wolves, the maintenance of core temperature was not always perfect; there was sometimes a drop of about 1°C as the experiment

progressed. Therefore the blood reaching the foot also became somewhat cooler. Despite this challenge, the foot pad temperature held level, indicating active control of blood flow in the service of local thermoregulation.

Local thermoregulation is supported by appropriate vascular specializations to ensure that warm blood reaches the places it is most needed, the outermost regions of the foot (Henshaw, 1978). The principal point, though, is that the foot pad is not always kept at 0°C. When in ambient air temperatures of ca. 20°C, the foot is relatively warm, around 25°–30°C. Stable foot temperature of 0°C, when the wolf's paw is in −30°C liquid, represents a change in the regulated level, initiated by external stimuli.

Once again change is not a failure of regulation but an adaptive response, promoting the survival of the animal. The wolf is able to reduce the dimensions of the conflict between preventing frostbite and conserving heat by having a local regulatory system for the foot, and being prepared to lower the set-point of that system when standing on a cold substrate. By minimizing heat loss through the extremities, rheostasis in the foot pad system actually contributes toward stability in the overall core temperature! Similar phenomena occur in other species enduring subfreezing temperatures: the Arctic fox, wolverine, polar bear, husky dog, caribou, reindeer, white-tailed deer and raven (Henshaw, 1986).

## COMPETITION BETWEEN LOCAL TEMPERATURE DEMANDS: SELECTIVE BRAIN COOLING

In the case of the wolf's foot pad, the local temperature regulator promotes thermal homeostasis of the animal's core. However, if there are separate regulatory systems for a variable in different parts of the body, then there is also the potential for types of interaction that induce conflict. Brain temperature is partly independently regulated and remains cooler than the trunk in hot animals. In some animals, artiodactyls for instance, cool venous blood from the nasal surfaces flows to the cavernous sinus at the base of the brain, where it encounters a rete carrying warm blood to the brain. This counter-current heat exchanger is not present in all mammals. Cerebral cooling can still be achieved simply by directing cool nasal blood to venous lakes lying at the base of the brain. In both cases nasal blood can also return to the heart via facial veins rather than via the cranial route used for brain cooling. A switching mechanism determines the distribution of blood between these two routes. This has been nicely visualized by cineangiography in the reindeer, *Rangifer tarandus* (Johnsen et al., 1987). During heat stress the facial vein contracts, directing more blood to the cavernous sinus heat exchanger. Occlusion of this route produces a rapid rise in brain temperature. However, the switch is not totally controlled by brain temperature. In hyperthermic conditions there is competition for the cooler nasal blood. For instance, in goats (*Capra hircus*) the extent of the brain cooling depends not only on the cerebral temperature but also on how warm the trunk is; when the main parts of the body are hyperthermic, the brain cooling is reduced (Caputa et al., 1986). It is suggested that the switching mecha-

nism determining the distribution of cool nasal blood between the brain and the trunk receives inputs from both these regions. At levels close to those where neuronal damage might result, defense of brain temperature becomes more important. In exercising oxen (*Bos taurus*) the brain stabilizes near 40.5°C while the body continues to rise to as high as 42.0°C (Chesy et al., 1985).

A switching mechanism does not necessarily entail rheostasis. We do not know whether the inputs from the different regulatory systems compete continuously at the level of the switch or modify the setting of thermoregulatory systems concerned with different parts of the body.

A curious case of selective brain cooling is that found in the rat after ejaculation (Blumberg et al., 1987; Blumberg and Moltz, 1988). The temperature of the medial preoptic region falls about 0.3°C and rises again during the next bout of mating. The effects are not merely due to changes in general motor activity; changes in the vasomotor tone in the nasal mucosa, and the consequent changes in availability of cool blood from this source, make an important contribution. The temperature of the body remains more stable than that of the preoptic area. Since the preoptic area is a site of a central thermostat, and since in this case its temperature is not driven directly by changes in the body temperature, it is possible that shifts in thermal set-point accompany mating. Perhaps these are hormonally induced. Testosterone often increases the firing rate of warm-sensitive neurons in the preoptic region (Boulant and Silva, 1988; Fig. 5–11). Another possibility is that, for some reason, nasal blood vessels must constrict and dilate before and after ejaculation, and that these changes drive those in preoptic temperature.

## SCROTAL WARMING

Warming of the sheep's scrotum results in large decreases, sometimes as much as 2°C, in core temperature (Waites, 1962). The magnitude of the effect depends on environmental temperature. Similar though less striking responses occur in the pig (Ingram and Legge, 1972). It is valuable to keep this part of the body cool because there are more abnormal sperm when it is hot (e.g., Cameron and Blackshaw, 1980); the ability of the epididymus to store sperm is compromised by temperatures prevailing in the abdomen (Foldesy and Bedford, 1982). Presumably this is why in many mammals the testes are not in close contact with the rest of the body. There are also numerous sweat glands (Blazquez et al., 1988), a vascular heat exchanger that serves to cool blood arriving from the rest of the body (Waites and Moule, 1961), and muscles that can adjust the closeness of the testes to the abdomen. These anatomical points make it plausible to suppose that there is a separate thermoregulatory system for this area. However, the matter remains problematic, there being different ways of accounting for the changes in core temperature resulting from scrotal warming.

One possibility is that scrotal afferents alter the set-point for core temperature. An alternative stems from conceptualizing temperature regulation in terms of a multiple-input system. In such a system extra importance could be given to the scrotal skin either by endowing it with more warm receptors or by

some central weighting, but it would still provide only one of many inputs. Hensel (1981) argued that with a multiple-input system any signal contributing to the feedback is part of the regulated variable. Therefore, temperature signals themselves cannot shift the temperature set-point: only nonthermal signals can do this. Recent electrophysiological work accords with the view that scrotal input combines with other thermal input. Preoptic neurones respond not only to scrotal warming but also to that of many other parts of the body. The responses to scrotal warming occur at lower thresholds (38°C) than those to warming the abdominal area (40°C). Nevertheless, the wide bilateral receptive fields of these neurones suggest that afferents from the scrotum are only a part of a regionally nonspecific system (Schingnitz and Werner, 1984). This view echoes Waites' (1976) remark that the scrotum must be "an important source of sensory information about the thermal environment . . . bringing benefits for general, as well as local thermoregulation." Playing a role in thermoregulation is not incompatible with scrotal warming also having general activating effects such as electroencephalogram desynchronization (Kanosue et al., 1985).

If it is only a matter of contributing to a common thermal signal, then scrotal warming should evoke the same *type* of response as warming other areas. The thresholds for scrotal warming could be different, and the magnitude of the response might be larger, but the type of response should be the same. With the local regulatory system for the goat's brain, the type of response produced by warming that area was different from the type of response produced by warming the trunk. In one case more blood was directed to the brain, in the other case more to the trunk. Regional information was conveyed. There was something more than a combination of all the inputs into some weighted value and a response that was then initiated on the basis of this amalgamated signal.

For scrotal temperature, it is not clear that there is a separate regulatory system with its own priorities. Nevertheless, it is not necessary to accept Hensel's (1981) argument that thermal stimuli cannot alter thermal set-points because they are part of the feedback signal. With collaterals they could perhaps both contribute to feedback and have other effects. It remains conceivable, therefore, that messages from the scrotum might alter set-point for core temperature.

## AUTOREGULATION OF BLOOD FLOW AND SUPPORTING MECHANISMS

If oxygen levels in a tissue fall, then blood vessels in that tissue dilate, bringing in more oxygen and other needed substances. This autoregulation of blood flow is a purely local phenomenon, although it may be supported by additional compensatory reactions involving other parts of the body. Autoregulation of blood flow is a further example of the existence of separate regulatory systems for a variable in different regions of the body. As with similar examples already given for temperature regulation (wolf's foot pad, selective brain cooling), the pos-

sibility arises of interactions and conflicts between the different local systems. For example, if muscle becomes active, using more oxygen, the dilation of its blood vessels could lead to drops in systemic pressure unless compensatory reactions, such as baroreceptor-mediated increases in heart rate, are brought into play. If one tissue begins to take more blood, this is bound to affect the circulation elsewhere in some way or another, even if only local mechanisms are involved in obtaining the extra blood in the first place. In fact, particularly important tissues do not rely only on their own autoregulation to battle it out with other tissues. They also recruit additional forces designed to influence circulation in other parts of the body. The renin–angiotensin system in the kidney and the CNS ischemic response are examples.

When pressure in the renal artery falls and blood flow through the kidney declines, renin is released from the kidney into the blood stream. The renin initiates a chain of reactions resulting in the production of angiotensin II in the lungs and other parts of the body. The angiotensin II causes vasoconstriction and an increase in arterial pressure. Independent of this change in blood pressure, angiotensin II resets baroreceptor-mediated decreases in heart rate toward higher pressures (Garner et al., 1987). These actions tend to restore flow through the kidneys. At the same time loss of water from the kidneys is reduced by other actions of angiotensin, for instance its stimulatory effect on adrenal output of aldosterone and the resultant decrease in water and salt loss from the kidney. The water retention and extra blood volume contribute to maintaining or raising the blood pressure. In this case the elevated blood pressure in the general circulation is imposed by the kidney on the rest of the body.

Similar dominance by a particular organ occurs during cerebral ischemia. When arterial pressure falls to very low levels (50 mm Hg), the vasomotor center in the brain directly and rapidly signals peripheral vessels to constrict. In some cases they become totally occluded, and systolic blood pressure may rise as high as 200 mm Hg. In cases like this, "when it is important to raise the arterial pressure temporarily, the nervous system can arbitrarily greatly decrease blood flow to major segments of the circulation despite the fact that the local blood flow regulatory mechanisms oppose this" (Guyton, 1982).

High pressure after cerebral ischemia or after drops in renal pressure involve conflict between different regulatory systems. In these conflicts, the brain, with its vasomotor center, or the kidney, with its renin–angiotensin system, have sufficient forces to overwhelm other systems. No evidence has been presented so far that there is any defense of different blood pressures. The kidney and the brain in these examples are not defending a higher pressure in the general circulation: they are using that higher pressure as an effector in defending their own blood supply. When the need for such defense ends, pressure returns to normal—for example, when a partially constricting clip is removed from the renal artery of an animal with one clipped kidney and one untouched kidney. However, in some circumstances there is a persisting defense of altered blood pressure. Baroreceptor resetting may support the maintenance of new blood pressures that were initiated in some other way, and high pressure may become institutionalized in structural changes. These

lines of evidence for rheostasis will be considered in the following two sections.

## BARORECEPTOR RESETTING: STABILITY AS AN END IN ITSELF

After brief periods of elevated blood pressure, the threshold pressure for activation of baroreceptor-mediated compensatory responses is higher than before the pressure was elevated (Fig. 5–14). This is called acute resetting of baroreceptors and baroreceptor reflexes. Similar resetting, but in the opposite direction, occurs after periods at decreased blood pressure. Acute resetting is distinguished from chronic resetting by its short time course. As little as 5 minutes is required for acute resetting, and the effect can be reversed in similar times (Kunze, 1985; Heesch and Carey, 1987). In some preparations resetting can even occur within 30 seconds (Burke et al., 1986). Recent papers talk of resetting as a continuous process (Burke et al., 1986; Kasting et al., 1987).

Since both short and long periods at altered blood pressure result in baroreceptor resetting, the distinction between acute and chronic resetting seems rather arbitrary. There is, perhaps, some value in making the distinction. In acute resetting structural changes such as thickening of arteries are ruled out. Such changes, whether primary or secondary, may be involved in the chronic resetting that occurs in hypertension. A second possible difference is that while in acute resetting the responsiveness of the reflex often remains the same (i.e., curves shifted to the right without a change of slope in Fig. 5–14), in chronic resetting there is commonly also a decrease in responsiveness (i.e., decrease

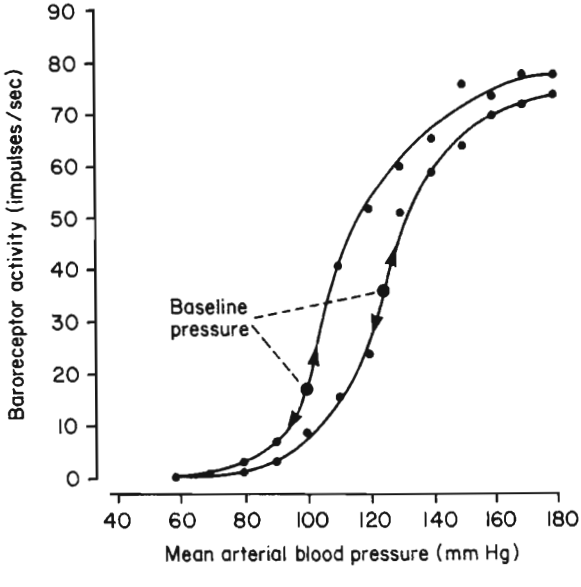



**Figure 5–14.** Resetting of aortic baroreceptors (action potentials from baroreceptor fibers) in dogs after 20-minute periods of baseline adaptation to pressures of 100 and 125 mm Hg. Resetting occurred both when pressures were increased from baseline (parts of curve marked with upward-pointing arrow) and when pressures were decreased (parts of curve marked with downward-pointing arrow). Dots show means. (Adapted from Coleridge et al., 1981. Operational sensitivity and acute resetting of aortic baroreceptors in dogs. *Circ. Res.* **48,** p. 681, by permission of the American Heart Association.)

in slope; e.g., Heesch and Carey, 1987; Sapru and Krieger, 1979). A further indication that acute and chronic resetting may be different is that acute resetting remains operative and normal in chronically hypertensive animals (Andresen, 1984; Heesch and Carey, 1987). That acute resetting occurs in similar fashion in both hypertensive and normotensive animals, despite the reduced distensibility of blood vessels in chronic hypertension, makes it seem likely that the underlying mechanisms are different in the acute and chronic cases. However, this argument depends on the assumption that distensibility, or other mechanical changes, do contribute to the resetting in chronic hypertension.

Baroreceptor resetting is an unusual and complex index of rheostasis in that, paradoxically, it appears that its main function is to preserve the stability of blood pressure rather than to initiate or support a change in this variable. In the case of blood pressure, stability in itself is of physiological value. For example, to prevent fainting when a person stands up it is important that the brain is buffered against sudden drops in pressure (Guyton, 1982). Whether the pressure was high or low, the same pressure needs to be maintained when the posture changes. This is not to say that there is no value in keeping mean arterial pressure for much of the time at a particular level, around 95 mm Hg in people, though the exact value may vary with age and other factors. But in addition to the value of defending particular pressures, there is also value in stability in itself, at least over short time spans (Kunze, 1985). "Acute resetting provides a family of buffer curves around a floating set-point, which allows the baroreceptor reflexes to maintain their sensitivity to increments in pressure over a wider range of base-line pressures than would otherwise be possible" (Heesch and Carey, 1987). Again, "baroreflex mechanisms function to limit variability of arterial pressure rather than to set its absolute level" (Kasting et al., 1987). That stability is one of the main functions of baroreceptors is consistent with the observation that after removal of sino-aortic baroreceptors, the average pressures settle down to relatively normal levels but variability is much increased (Cowley et al., 1973). In some experiments, however, pressure is higher after baroreceptor denervation. To what extent this is a temporary phenomenon or occurs because taking measurements has a greater effect on animals lacking their pressure-buffering systems remains controversial (Cowley, 1981; Scher, 1981).

Baroreceptors probably detect stretch rather than pressure directly. Like other stretch receptors, they adapt to continued stimulation. Adaptation of stretch receptors and resetting may appear to be merely two ways of describing the same phenomenon. Some of the resetting is probably a property of the baroreceptor or its immediate environment. It can take place *in vitro* (e.g., Andresen, 1984). However, there is evidently also a central component. The amount of resetting of reflexes (e.g., blood pressure change, sympathetic discharge) is greater than the amount of resetting in the firing rate of nerves in the afferent limb of the reflexes from the baroreceptors. Also, if these nerves are cut, and electrically stimulated on the central side of the cut, resetting still occurs, even though the baroreceptors have been left without a way of influencing the CNS (Kunze, 1986). There is more to resetting than adaptation of stretch receptors (see also Tan et al., 1989). Whatever the mechanism, resetting

of baroreceptor reflexes to higher values widens their operating range (Kunze, 1985; Korner, 1988). Resetting to low values does the same by preventing low pressures from lying below the thresholds for responses. Resetting, therefore, permits baroreceptors to make a greater contribution toward stability of blood pressure than would otherwise be possible.

Resetting does not itself initiate a change in regulated levels, but it supports the maintenance of a change that has occurred in some other way. Baroreceptor reflexes help to defend a different blood pressure level. Even though the function of baroreceptor resetting is probably not to defend a different level so much as to defend stability per se, its presence is an indication that rheostasis has occurred.

Nevertheless, as a defense baroreceptor resetting is—if one may use the expression—"half-hearted." In acute resetting of the curves for baroreceptor firing or for reflex responses, the shift is often less than half that of the amount of change in the pressure. Perhaps the function of incomplete resetting is to continue to provide some information about deviations from normal mean pressures (Kunze, 1985).

An interesting exception to incomplete resetting comes from a study on changes in human heart rate in response to brief pressure stimuli around the neck. The complete resetting in this case took place during variations in blood pressure over a 40 mm Hg range occurring spontaneously through the course of the day. In contrast, in many studies on animals, resetting has been produced by artificially raising or lowering the pressure. Perhaps during spontaneous changes within the normal range information about deviations from mean pressure is not required. Perhaps there is no deviation if set-point for arterial pressure changes spontaneously. In any case, as Kasting et al. (1987) say, "the emphasis of much of the earlier work has been upon experimentally or genetically induced arterial pressure changes, and the resetting process has been regarded as a pathological adaptation," but their results support the view that "baroreceptor resetting is a physiological as well as a pathological process." Coleridge et al. (1981) make the same point: "Resetting has been regarded as an early manifestation of an essentially pathological process. Our results suggest that resetting is not necessarily confined to the long term, but may occur within a matter of minutes. As such it may represent an integral feature of baroreceptor operation in normal circumstances."

## HYPERTENSION AND STRUCTURAL CHANGES

After periods at high blood pressure, the structure of arteries may change in ways that prolong and sustain the hypertension. Work by Sapru and Krieger (1979) on a strain of rats that become hypertensive spontaneously illustrates this phenomenon. Untreated rats developed systolic blood pressures of 260 mm Hg by about 7 months of age, while animals of the same strain treated continuously with antihypertensive drugs remained normotensive. In the hypertensive group there was a thickening of the tunica media layer of the aorta and a

decrease in distensibility of the aortic wall. There was also a resetting and blunting of the baroreceptor response from aortic nerves. These phenomena all appear to go together. Increased wall thickness would decrease distensiblity, and decreased distensibility would mean that higher pressures were needed to stretch the aorta enough to stimulate baroreceptor firing. However, resetting of baroreceptors, though not as great, was also found in rats without these structural changes. These rats had been kept on the antihypertensive therapy, but it had been withdrawn 2 weeks before the measurements. Their systolic pressure averaged 220 mm Hg even though aortic thickness and distensibility were normal. So in this case the structural and mechanical changes are evidently secondary to hypertension. But once the changes have occurred they help sustain hypertension. The degree of baroreceptor resetting after antihypertensive treatment correlates with regression of the vascular changes, not with how much the blood pressure is reduced. Lowering of pressure to normotensive levels does not always reverse the hypertensive resetting. In rats that have been hypertensive for long durations, there is less restoration toward normal values. Structural changes are less likely to be reversible if hypertension has lasted a long time (Sapru and Wang, 1976). In contrast, however, in rats that have been hypertensive insufficiently long (2 weeks) for the vascular changes to occur, there is only partial baroreceptor resetting, and antihypertensive drug therapy rapidly restores the blood pressure to normal levels (Sapru and Krieger, 1979).

There are, of course, numerous different animal models of hypertension and the types of structural change are different. For instance, while hyperplasia of smooth muscle in the media of some arteries is common, the presence of hypertrophy of these cells is more variable (Lee, 1987). Although Sapru and Krieger (1979) did not find changes in arterial thickness and distensibility before hypertension had persisted at least 2 weeks, they pointed out that subtler structural changes might have been detected by other methods. Indeed, smooth muscle cell hyperplasia has been detected in the prehypertensive stage of rats that eventually became hypertensive spontaneously (Lee, 1987). The question of whether changes in structure are primary and causal or secondary to the high pressure is deceptively simple; its answer may depend on the particular structural change being measured and on the etiology of the hypertension.

In those cases in which structural changes, whether primary or secondary do occur and do help to sustain high blood pressure, there is a defense of an elevated pressure. Rheostasis has occurred. Even though acute baroreceptor resetting is still possible in the hypertensive state, as mentioned in the last section (Andresen, 1984; Heesch and Carey, 1987), such resetting is incomplete. Therefore, the baroreceptors still become locked into defending higher than normal levels of blood pressure by structural changes such as reduced distensibility. The idea that irreversible or slowly reversible changes in the vasculature sustain high blood pressure through baroreceptor resetting is common in the contemporary literature on hypertension (e.g., Cox and Bagshaw, 1988).

In the context of other examples of rheostasis, it is not so much the higher blood pressure itself as the difficulty in reversing a hypertension institutional-

ized in structural changes that gives it a pathological aura. Also, to the extent that hypertension results from dietary effects on arteries and their distensibility, this seems pathological. However, some kinds of high blood pressure need not necessarily be considered as merely pathological but may also be seen as compensatory and successful blood flow regulation by important organs.

## NEUROGENIC HYPERTENSION

Previous sections on blood pressure have covered an indirect way in which hypertension arises. Autoregulatory needs of a particular tissue can force blood pressure up; the higher levels are then sustained by baroreceptors and eventually established by structural vascular changes. Hypertension can also arise in a more direct way, as happens in neurogenic hypertension. The evidence has been assembled by Julius (1988), who argues that there is a category of hypertension in which the ability to regulate blood pressure is normal but the set-point is elevated. This implies that systemic blood pressure is a regulated variable. Let us examine this last point first.

To maintain adequate circulation to the tissues, regulatory responses must come into action whenever circulation is inadequate. However, the ultimate aim of maintaining blood flow to the tissues could still be achieved, even if flow itself were not the regulated variable. Since flow = pressure/resistance of the blood vessels, the CNS might be sensitive to and respond to pressure or resistance instead. Julius (1988) argues that in fact the CNS is responsive to pressure changes. He marshals a number of examples where pressure remains relatively constant despite changes in flow or resistance. For example, blood pressure remains almost constant when cardiac output is reduced by administering the beta-adrenergic blocker propranolol. Resistance increases by an amount just enough to balance out the decrease in cardiac output (Julius et al., 1971). Another circumstance in which reduced cardiac output is offset by increased resistance is when someone stands up. When this happens the blood pressure actually increases. Expressed as percentage of change, this pressure increase, 10%, is sometimes almost as great as the drop in cardiac output, 12% (Julius et al., 1971). In this example inferences about which is the regulated variable cannot justifiably be made on the basis of constancy alone. However, as Julius (1988) points out, there is no a priori reason why the response to standing up is such as it is. The orthostatic challenge could have been met by changes in the venous return and a decrease in resistance, leaving pressure lower than before. But the observed response to upright posture is a maintenance (in fact an increase) of blood pressure, with a reduced cardiac output. This is not inconsistent with pressure being regulated and defended. Perhaps there is a small increase in the pressure set-point to compensate for the gravitational decrease of blood pressure to the head.

In these examples, pressure was only measured during short-lasting experiments conducted in standardized conditions. Blood pressure measured in more natural circumstances over the course of a day is by no means constant. It is common for values at the high end of the daily range to be 50% above

those at the low end of the range (Bevan et al., 1969; cf. Broten et al., 1988). Pressure rises during emotional states; simply doing mental arithmetic is enough. If blood pressure is the regulated variable, are these neurogenic increases in blood pressure examples of rheostasis? This seems likely because, if one effector mechanism is blocked, then another effector produces the pressure increase instead. For example, blood pressure increases during an interview in which subjects are required to talk about their everyday life, even when attempts are made to avoid stress. The pressure increase still occurs when augmented cardiac output is prevented by beta-adrenergic blockers. The pressure change is mediated instead by an increase in resistance (Fig. 5–15; Ulrych, 1969). Further examples of a shift to a high resistance response are given by Julius (1988), who comments, "cumulatively, all these examples indicate that . . . the pressor response is centrally integrated and, depending on the circumstances, the autonomic tone will be shifted throughout the cardiovascular system in order to achieve the desired increase in blood pressure."

If pressure is the regulated variable, and if neurogenic pressor responses represent an elevation in regulated level, then for hypertension to result the only additional requirement is that the neurogenic responses persist. Neurogenic effects are presumably mediated by the sympathetic nervous system. At least, there are a number of animal preparations in which sympathetic tone has been clearly implicated in hypertension. For example, neonatal chemical sympathetic denervation in strains of spontaneously hypertensive rats keeps their blood pressure in the normotensive range (Lee et al., 1987). This is an example of how sympathetic tone can be important in the initiation of hypertension. However, if secondary arterial thickening takes over the maintenance of higher pressures, then enhanced sympathetic activity would no longer be needed to meet the demands of an elevated set-point. Therefore, a lack of increased sympathetic tone during established hypertension does not disprove a neurogenic origin; on the contrary, it is to be expected on a set-point interpretation pro-

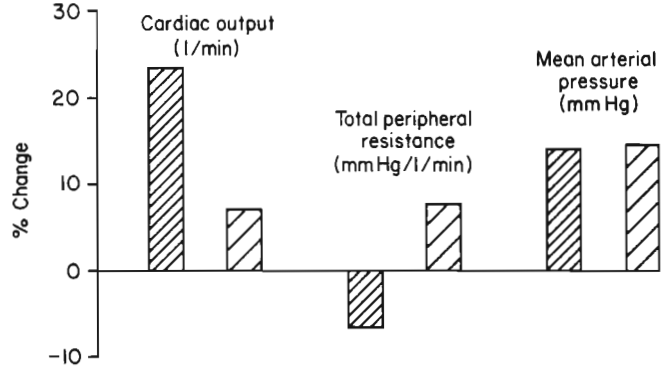



**Figure 5–15.** Mean percentage change over quiet baseline conditions of cardiac output, vascular resistance, and blood pressure during an interview requiring speech (densely cross-hatched bars) and during a similar interview after receiving a beta-adrenergic blocker (sparsely cross-hatched bars) (data from Ulrych, 1969).

vided that vascular or other changes sufficient to maintain the higher pressure have occurred (Julius, 1988).

Whether or not the origin of many cases of hypertension is neural and mediated initially by the sympathetic system, the evidence suggests that, at least in some types of hypertension, there is indeed a defense of the elevated blood pressure. Patients with mild hypertension are capable of increasing and decreasing their cardiac output and resistance—the latter effector is especially used. They respond to sitting up, exercise, propranolol, and experimental expansion of blood volume, but in all these situations they maintain their pressures above those of controls (Julius et al., 1971). "Consequently, it appears that hypertension is not a disease of blood pressure regulation. The pressure is set at a higher level and around that setting it is regulated in a normal fashion" (Julius, 1988).

## SUMMARY

Rheostasis is a common reaction to stressors such as pathogens, injury, psychogenic stress, water shortage, and food deprivation. There are numerous examples of alterations in thermal and hormonal regulation during food deprivation. Reproductive and metabolic shut-down can be viewed as effector mechanisms in the body fat regulatory system, which takes priority in undernourished animals.

Defended levels sometimes shift rapidly, within hours or less. Reactive rheostasis may have survival value in attenuating the stress. It is also involved in the gradual adaptation to physical work and to high altitude.

Separate regulatory systems for a given variable in different parts of the body provide possibilities for interregional conflicts. Changes in regulated levels of blood pressure and temperature are sometimes related to local needs.

Rheostasis may persist and become very difficult to reverse if supported by structural changes.

## PREVIEW

Programmed and reactive rheostasis have been covered in the last two chapters. There remain some interesting combinations of these two categories to be considered in the next chapter.

# 6

# Second-Order Rheostasis

If we set up judges, then who shall judge the judges? The same problem arises in regulatory physiology. If there are systems that maintain variables at consistent levels, systems—be they based on negative feedback or on some other organization—that act as if they included a set-point, then that presents a possibility for the evolution of additional mechanisms that adjust the value of the set-points, i.e., for systems mediating rheostasis. As Cabanac and Russek (1982) have put it, "on peut dire que l'homéorheusie [rheostasis in this book] est la capacité de l'organisme à contrôler son homéostasie." But then these superimposed controlling systems themselves become a target for still further controls, and the possibility arises for second-order rheostasis, that is for modulation of the way or the rate at which rheostasis is altering the set-point of the basic regulatory systems. There are some phenomena that appear to exemplify this possibility, although until they are better understood it cannot be excluded that they arise in some other way.

## CATCH-UP GROWTH IN JUVENILES: EFFECTS OF IRRADIATION

After temporary retardation in growth by a passing illness or food restriction, there is a period of accelerated growth in young animals or children until they attain normal body size for their age. This has been called "catch-up growth" by pediatricians (Prader et al., 1963) and "compensatory growth" by biologists (Wilson and Osbourn, 1960). Mosier (1986) reviews the history and the current status of work on this topic. The central concept is the postulation of a comparison between a signal indicating the actual size (or height) and the programmed information about the size (or height) for that age (Tanner, 1963). This is equivalent to saying that there is a set-point, a term used later in this literature (e.g., Mosier, 1986). This formulation of catch-up growth is supported by the reverse phenomenon of catch-down growth. For instance, when growth hormone treatment is stopped, growth rates of genetically small children fall to

almost zero (Tanner et al., 1971). Deceleration of growth also can occur after treatment of congenital adrenal hyperplasia, a condition that results in rapid growth and precocious maturation (Bongiovanni et al., 1973). These types of effect could probably be much more easily studied in animals and might provide firmer evidence for the phenomenon of regulatory deceleration of growth.

Catch-up growth is demonstrable at various ages and sizes, implying that the set-point must alter. This aspect of the phenomenon could have been included as a further example of programmed rheostasis in Chapter 4. However, it happens that it is possible to alter the rate at which the programmed changes occur. Irradiating the head of 2-day-old rats with X-rays retards subsequent growth. If this was all that was known, the explanation might simply be that there was damage to the effectors required for faster growth. Additional experiments show that this is not the case. When neonatally irradiated rats are fasted for 48 hours at the age of 40 days, their body weight drops and their rate of tail growth declines. On refeeding, body weight gain and tail growth accelerate and the animals catch up to the curve for nonfasted irradiated animals (Mosier et al., 1983; Fig. 6–1). Effectors for faster growth are present in the irradiated rats but are normally not called up to work at full capacity. Some further facts suggest that irradiation produces a relatively specific change. First, growth hormone secretion is not impaired; frequency, amplitude, and duration of growth hormone surges are the same as in control animals (Mosier et al., 1986). Second, to produce stunting, it is not necessary to irradiate the whole head; it is sufficient to treat just a narrow band in the midline (Mosier and Jansons, 1970). "The results of these experiments are compatible with, but not necessarily limited to, the possibility that an age-dependent set-point mechanism for body size exists in the central nervous system of the rat and that the set-point is altered

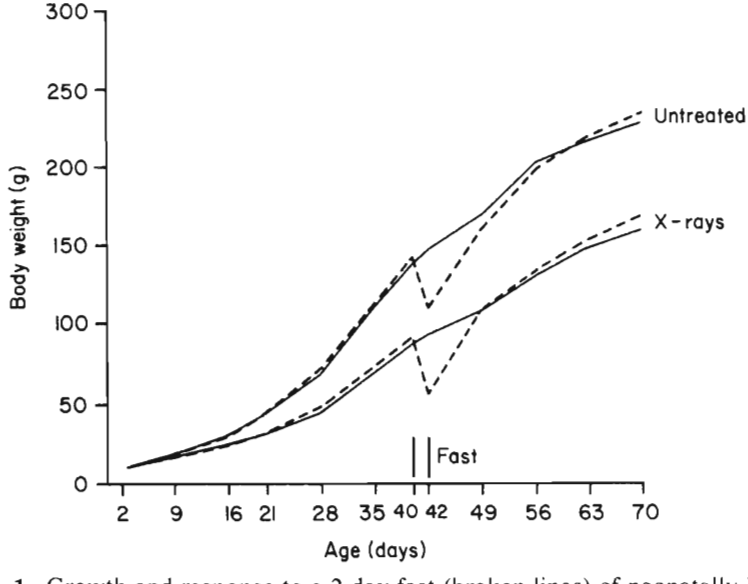



**Figure 6–1.** Growth and response to a 2-day fast (broken lines) of neonatally X-irradiated rats and untreated controls (adapted from Mosier et al., 1983, *Growth* **47,** p. 18).

by neonatal head-irradiation" (Mosier et al., 1983). But it is not just the set-point that is altered, it is also the rate of change of the set-point with age.

## DORSOMEDIAL HYPOTHALAMIC LESIONS

The area of the brain irradiated in the Mosier et al. (1983) experiment included the dorsomedial hypothalamic nuclei. This is of interest in that lesions in this region result in decreased growth rates. Moreover, presenting challenges to rats with such lesions shows that regulation is still present, as it is in X-irradiated rats (Bernardis et al., 1988). However, it has been argued (Bernardis et al., 1988) that there may be dissimilarities between these two syndromes in that in the X-irradiated animals some organs are heavier than normal as a percentage of body weight, whereas this is not the case for most of these organs after electrolytic lesioning of the dorsomedial hypothalamus.

## FAT DEPOSITION IN ADULTS: VENTROMEDIAL HYPOTHALAMIC LESIONS

After lesioning of the ventromedial area of the hypothalamus, body weight rises steeply. This is the dynamic phase of hypothalamic hyperphagia after which weight gain slackens. On the basis of experiments demonstrating defense of higher weights in rats (Hoebel and Teitelbaum, 1966; Barnes and Mrosovsky, 1974), these effects can be described in terms of sudden lesion-induced elevations of the set-point for fat, although the underlying mechanisms may more probably be a change in an open loop factor such as increased responsiveness to palatable or salient food (Keesey, 1978; see also Mrosovsky and Powley, 1977). It has recently been discovered that, in addition to the steep rise during the dynamic phase, there is also an increase in the rate of subsequent body weight gain. Rats with ventromedial hypothalamic lesions do not, in fact, reach a plateau in body weight. They show a gradual and continuing linear weight gain; the slope of this gain is steeper than in control animals. This becomes evident when animals are studied for long periods without introducing manipulations (Fig. 6–2). Because tibia and body lengths do not change, it is inferred that this continued weight increment represents fattening (Hallonquist and Brandes, 1984). These findings suggest that the lesions have two separate effects on body weight: an immediate elevation of the regulated weight and an increased rate of gain subsequently. There are no significant correlations between the extent of these two effects (Hallonquist and Brandes, 1984).

The linear phase in lesioned animals represents a change in the rate at which the set-point climbs. If the lesioned animals are brought down in weight to control level by feeding them limited rations for 6 weeks, then on refeeding *ad libitum* their weight rises steeply until it reaches the projection of the pre-deprivation line (Fig. 6–2). These findings "indicate that the set-point for body weight was actively regulated and continued to climb during the period of food restriction and recovery of weight. If the linear phase of fattening observed did not reflect a continuously climbing set-point independent of actual food intake

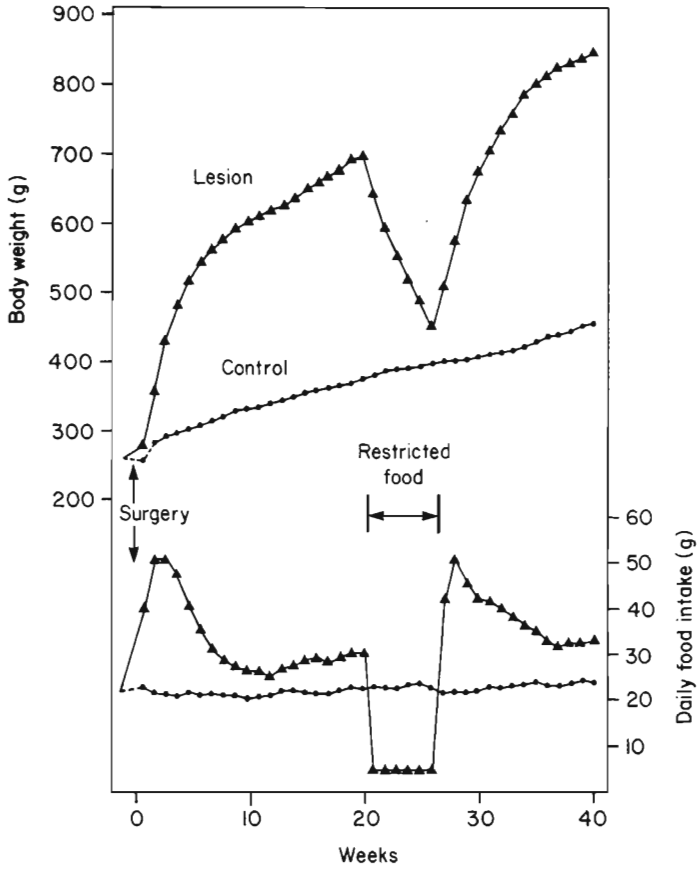



**Figure 6–2.** Body weights and food intakes of rats with ventromedial hypothalamic lesions and of sham-operated controls. (Adapted from Hallonquist and Brades, 1984, Ventromedial hypothalamic lesions in rats: gradual elevation of body weight set-point. *Physiol. Behav.* **33,** p. 832. Copyright 1984, Pergamon Press, PLC.)

and body weight, but reflected only a passive, constant daily error in weight regulation or the maximum rate at which weight can be gained over such body weights, then the rates of weight gain in the linear phase prior to food restriction and over the same weight range following release from food restriction should have been similar" (Hallonquist and Brandes, 1984).

## LATERAL HYPOTHALAMIC LESIONS: BODY WEIGHT CHANGES

Damaging the lateral hypothalamus results in aphagia and weight loss, until a new lower level of weight is reached. Food intake then recovers to a value metabolically appropriate for the new lower weight. Both compensatory changes in intake and in energy expenditure come to the defense of the new lower weight level after challenges. This is one of the best researched and clear-

est examples of a change in defended level (Keesey, 1978; Keesey and Powley, 1986). Most attention has been focused on the immediate decrease of set-point after the lesion. However, in addition to this there is a decline in the rate of gain over at least the subsequent 5–6 months (Keesey, 1978). The weight trajectories of lesioned and control rats diverge. Information about body composition over this time span is not available, and it is not clear what is the regulated variable, only that it is something correlated with body weight. However, it is clear that lateral hypothalamic lesions not only produce an immediate drop in set-point but also a change in rate of subsequent weight gain.

## PREOPTIC LESIONS: EXAGGERATED DIURNAL TEMPERATURE CYCLES

After medial preoptic lesions in rats, the amplitude of the diurnal temperature cycle increases from about 1.5°–2.0°C to as much as 4.0°C. The changes at the peak are especially prominent, with temperatures going to 40.0°C or more. The lesioned rats defend their high temperatures at this phase: when put into a situation in which they have to press a bar to escape or avoid cold air, they do not let themselves cool down to normal values but actively maintain the elevated levels by their behavior (Szymusiak et al., 1985). In this example, indomethacin, a prostaglandin inhibitor, brings the lesion-induced fever down as it does a pathogen-induced fever (Levy et al., 1987). The rheostasis is consequent on the lesion, but what changes is not just the defended temperature but the characteristics of the circadian cycle of set-points as well.

## PRECOCIOUS AND DELAYED PUBERTY

It is possible to advance or delay the onset of puberty. Treatment with dopamine receptor blockers produces precocious puberty. The treatment also hastens the decline of the suppressive effects of estrogens on luteinizing hormone (LH) secretion (Andrews et al., 1981). Putting rats on limited rations postpones puberty; food deprivation sufficient to delay vaginal opening from day 39 to day 52 also increases the suppressive effects of estrogens in prepubertal animals tested on days 32–36 (Piacsek, 1985). Likewise in lambs, undernourishment forestalls the response to estradiol until past the age when estrous cycles appear in animals fed *ad libitum* (Foster and Olster, 1985). So while rheostasis occurring at puberty is developmentally programmed, the timing of this event is subject to higher order controls.

## SECOND-ORDER RHEOSTASIS: UNNECESSARY CONCEPT BUT LOGICAL POSSIBILITY

It is not claimed that categorizing the phenomena described in this chapter as examples of second-order rheostasis is the only, or even the best, way to think about them. Cycle amplitudes change in a variety of circumstances. The ten-

dency for lowering of body temperature during malnutrition to be most pronounced during the sleep phase of the circadian cycle, and the greater amplitude of the temperature rhythm in the dehydrated camel have already been mentioned in Chapter 5. Is anything gained by labeling a change in cycle amplitude of a defended variable as second-order rheostasis? It may simply be that some interactions between a cyclical program for set-point, and a changed physiological state result in a different cycle amplitude. Or it may be that a change in responsiveness to direct effects of light and dark on a variable may exaggerate the amplitude of diurnal cycles. The change may not necessarily be in an endogenous cyclical program for altering set-points over a 24-hour span. Likewise, a change in growth trajectory may not be a change in a program, some redigging of a Waddingtonian canal (Waddington, 1957). Rather, the change may be in some variable that interacts with a developmental program, with the result of this interaction differing progressively from control levels during ontogeny.

These disclaimers notwithstanding, second-order rheostasis is a logical possibility. The aim of this short chapter is to point out, with a few examples that give life to the idea, but do not prove it, that once mechanisms modulating set-point exist, there always arises the possibility of superimposed additional mechanisms, modulating the modulators. Whether such mechanisms actually exist and are deployed in natural circumstances remains unclear. Many of the examples in this chapter concern changes after physiological insults such as irradiation and brain lesions. They do not, therefore, add to the argument advanced in earlier chapters that rheostasis frequently has adaptive value.

## SUMMARY

Theoretically, there might exist higher order controls that altered the rate or time at which rheostatic mechanisms themselves adjusted set-points. Some possible examples of such second-order rheostasis are alterations in growth rate trajectories, rhythm amplitudes, and the timing of developmental changes at puberty.

These examples conclude the presentation of situations in which the regulated level of a variable appears to change (Chapters 4, 5, and 6).

## PREVIEW

It is now time to tackle, or at least admit, some of the problems about the concept of rheostasis as a way of thinking about such diverse phenomena.

# 7

# Problems and Cautions

## OUTCOMES VERSUS MECHANISMS

The previous chapters of this book have presented rheostasis in terms of the phenomena observed rather than in terms of underlying mechanisms. They have described changes in regulated level and said that there has been a change in set-point when it appears "as if" such a change had taken place. Taking this approach, one may find enough examples of rheostasis to become convinced that the body is not always trying to control variables within particular narrow ranges. There is more to physiology than maintaining constancy.

Examples of rheostasis have been classified on the basis of the circumstances in which they occur, with an attempt to discover the possible survival value of forsaking regulatory constancy. Of course, to a large extent lack of knowledge makes classification in terms of mechanisms premature. However, even if we knew much more about the underlying mechanisms, I am not sure that I would take a different approach or advocate abandoning a descriptive use of set-point changes.

To other investigators this stance may seem highly unsatisfactory. Many of those with an appreciation of control systems would undoubtedly prefer (e.g., Toates, 1983), or even insist on, reserving a term like *rheostasis* for cases where it is clear that changes in response to feedback are causal in changing the level of the regulated variable. Some specific examples, the increase of body temperature during exercise and the dependence of body weight on palatability of the diet, illustrate the problems in a descriptive use of the term *set-point*.

## HYPERTHERMIA DURING EXERCISE

During physical activity, heat production by the muscles increases greatly. Body temperature rises and levels off at a value that appears to be relatively independent of environmental temperature. In 1938 Nielsen proposed that this represented a change in regulation. The alternative view is that the higher tem-

peratures reflect a failure to dissipate the extra heat. Compensation for any disturbance to a negative feedback system is never complete, even when the open loop gain is high (see Box, pp. 127–129, for explanation of terms). In the case of exercise the disturbance can be considerable: heat production by the muscles can increase by an order of magnitude. The two views of exercise hyperthermia are shown in Figure 7–1.

In recent years the second view, that activity simply produces too great a heat load to be compensated for by a set-point that remains the same, has been more widely accepted. Among the supporting arguments are these: (1) Close inspection of Nielsen's (1938) data reveals that the temperature levels reached during exercise were slightly different at different environmental temperatures (Brengelmann, 1977). When exercise takes place in cool water, the increases in body temperature are much less (McMurray and Horvath, 1979). Even when minimal or no effect of ambient temperature on the amount of exercise-induced hyperthermia is found, this does not prove that set-point has risen; it can be explained by the influence of skin temperature on sweating (Davies, 1979). There is more sweating in a warm environment than a cool one, even when core temperatures are the same. (2) Exercise results in alliesthesia, with cooler skin temperatures becoming more pleasant, though not immediately but only after internal temperatures begin to rise (Cabanac et al., 1971a). This finding is consistent with exercise creating a discrepancy between the actual temperature and a set-point that remains unaltered. (3) Prostaglandin inhibitors do not block exercise-induced hyperthermia (Downey and Darling, 1962). The increase in body temperature is, therefore, different from fever. (4) Absence of a set-point change may be inferred from studies of the rate of sweating as a function of body temperature. Figure 7–2 shows some different possibilities for the response of a heat-dissipating effector as a function of temperature and exercise.

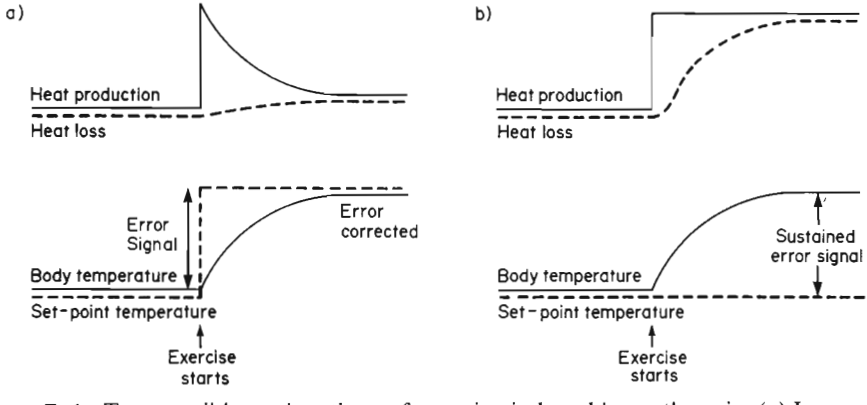



**Figure 7–1.** Two possible explanations of exercise-induced hyperthermia. (a) Increased heat production follows a change in set-point. (b) Set-point remains the same, but heat loss increases in proportion to the difference between the actual and the set-point temperature until equality between heat loss and heat production prevents further changes in temperature.

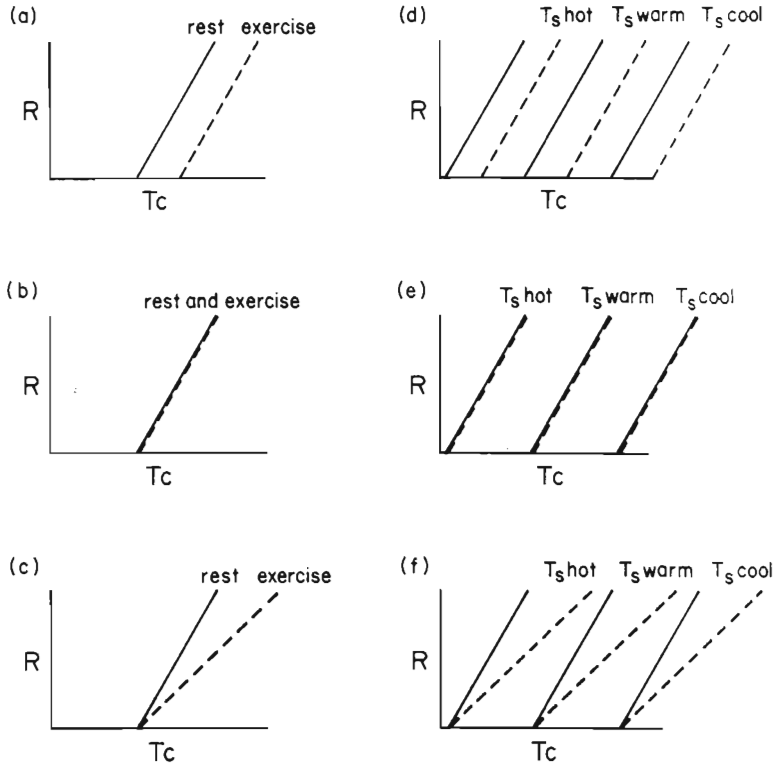



**Figure 7–2.** Some possible relationships between the response (R) of a heat-dissipating effector and core temperature ($T_c$) during rest and exercise. Parts a–c show the relationships for one skin temperature; Parts d–f for three different skin temperatures ($T_s$ hot, $T_s$ warm, $T_s$ cool). Parts a and d suggest a set-point elevation during exercise; b and e suggest that exercise has no influence on the thermoregulatory system; and c and f suggest that there is a decrease in gain during exercise.

If the set-point rises during exercise, then the whole line should be shifted to the right but the slope should remain the same (Fig. 7–2a). If exercise (a non-thermal factor) does not alter the regulatory system, then the line should remain in the same position: the response should be a function only of thermal factors (Fig. 7–2b). Another possibility is that there is a change both in threshold and in gain, in which case the slope will alter, as in Figure 7–2c. The situation is even more complex because skin temperatures must also be taken into account; there should be a number of lines, one for each different skin temperature (Fig. 7–2d, e, f). In fact there are data on sweating rate that are fairly similar to Figure 7–2e (Nadel et al., 1971). The higher internal temperatures were a result of bicycling (though actual measurements were made shortly after exercise, while the subjects lay down). Sweating rates at these high temperatures fitted on the same lines as the rates at lower temperatures. Overall, then, there is a good case against there being an elevation of set-point during exercise.

Nevertheless, a number of investigators remain uncertain about the matter. For instance, Brengelmann (1977) has pointed out that sweating is sometimes influenced by the rate of change of skin temperature, as well as by the actual skin temperature. It is important, therefore, that steady states are reached during experiments or that transient effects are incorporated into the modeling; these requirements have not always been met. Also the findings on another heat-dissipating effector, the blood flow in the skin, are less consistent. Brengelmann (1977) cautions that there may be a difference of >0.5° C in the core temperature threshold for increased blood flow when identical tests are made on different occasions. And, commenting on findings that core temperature and skin temperature can account for 80% of the variation in sweating rate during rest and exercise, Gisolfi (1983) asks: "What about the other 20%? Is it thermal or non-thermal?" Perhaps there is some non-thermal input from the muscles at the start of exercise, before the body becomes hotter. It is also questionable whether the failure of prostaglandin inhibitors to block exercise-induced hyperthermia is critical evidence against there being an elevation in regulated level. For this to be the case, it must be assumed that prostaglandins guard the only door to the thermal set-point. Even for fever itself, it is debatable whether prostaglandins are essential (Mitchell et al., 1986).

Further complications concern what happens after exercise. Body temperatures and thresholds for sweating remain about 0.35° C higher than normal for several hours in people after a 37 km walk (Haight and Keatinge, 1973). An hour of work on a bicycle ergometer results in the release of some substance that is pyrogenic when injected into rats (Cannon and Kluger, 1983). The distinction between during and after exercise is not necessarily satisfactory. If the subjects in this experiment had bicycled for another hour, would the release of pyrogen have been postponed until they stopped? This seems unlikely, especially if these pyrogens are released as a result of minor tissue damage during exercise, as has been suggested (Haight and Keatinge, 1973). It is premature, therefore, to rule out the possibility that with certain types of durations of exercise a component of the temperature rise might be similar to fever and be regulated (see also Wyndham, 1973).

On balance, however, more evidence exists that temperature regulation during exercise is not different from that at rest and that set-point remains the same (Davies, 1979; Stitt, 1979; Hensel, 1981; Gisolfi, 1983). If this is the case, then exercise hyperthermia does not result from a discrepancy between a set-point elevated by exercise and the actual temperature at the onset of exercise; in terms of causality, the phenomenon is not the result of a set-point change but of heat production acting simply as an open-loop factor or disturbance. Even though it might sometimes look as if set-point had been elevated, it can be argued that this should not be included as an example of rheostasis.

Finally, it should be noted that the extent of the problem of set-point versus open-loop changes during exercise may have been exaggerated because selective brain cooling often keeps cerebral temperature below that of the trunk and close to normothermic levels. Since the brain contains the thermostats, if its temperature does not rise, then there is no change in the regulated variable to be explained (Cabanac and Caputa, 1979). This may resolve the problem for

short bouts of exercise but it remains to be demonstrated that brain temperature can really be kept normothermic during prolonged strenuous activity. In fact, the degree of selective brain cooling depends on how warm the trunk becomes (Caputa et al., 1986).

### Open Loop Gain and Error Attenuation

In the negative feedback system shown in Figure 7–3a, the value that the regulated variable settles at depends both on the strength of disturbances on the effector systems (or directly to the regulated variable itself) and on the strength of the messages derived from the error signal, i.e., the compensatory responses. The importance of the latter can be increased by placing an amplifier between the error signal and the effectors (Fig. 7–3b). The greater the amplification, the better the system can compensate for disturbances. The ability to compensate can be quantified by a term called the *open loop gain*, or *loop gain* of the system.

When a disturbance to the system occurs, the value of the regulated variable changes. Following Houk (1980) and others, this change can be divided into two components: the amount that would occur as a result of the disturbance in the absence of feedback (Dist), and the amount that occurs as a result of the compensatory action (Comp). The actual change in the regulated variable ($d_{reg}$) is the difference between these two components.

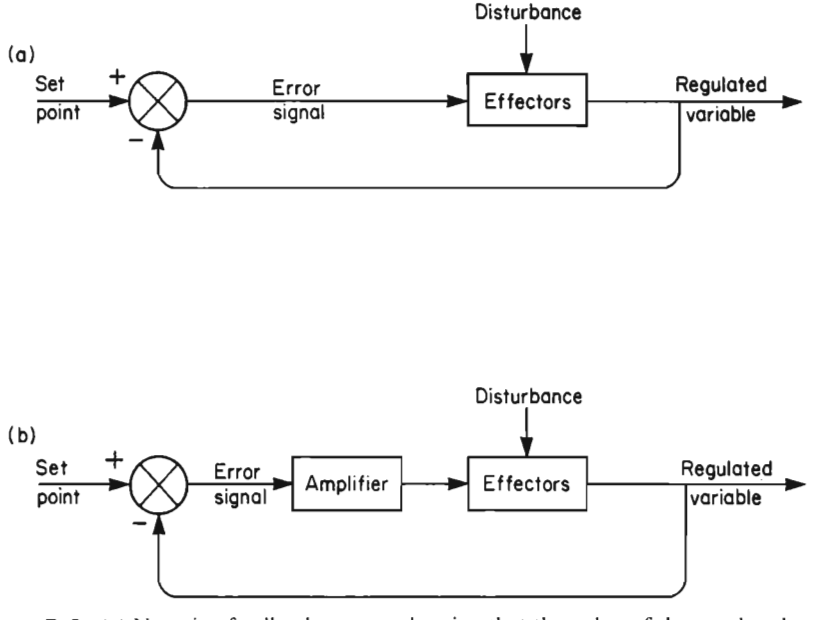



**Figure 7–3.** (a) Negative feedback system showing that the value of the regulated variable depends on both the error signal (compensatory component) and the disturbance. (b) An amplifier has been inserted to increase the influence of the error signal.

$$d_{reg} = \text{Dist} - \text{Comp} \tag{1}$$

The open loop gain (G) is defined as the amount of change attributable to compensation compared to the total change actually seen.

$$G = \frac{\text{Comp}}{\text{Dist} - \text{Comp}} \tag{2}$$

Since the gain is a ratio, there are no units.

It is now possible to express the change in the regulated variable ($d_{reg}$) in terms of only the disturbance change and the open loop gain. Equation 2 is rearranged to give:

$$\text{Comp} = \frac{G \times \text{Dist}}{1 + G} \tag{3}$$

Substituting this from equation 3 for Comp in equation 1:

$$d_{reg} = \text{Dist} - \frac{G \times \text{Dist}}{1 + G}$$

This may be rearranged to:

$$d_{reg} = \frac{\text{Dist}}{1 + G} \tag{4}$$

Evidently, the higher the gain (G), the less the regulated variable will change in response to a disturbance. If the gain is extremely high, the disturbances will cause practically no change. However, in practice there are reasons why the gain cannot be too high. Compensatory responses cannot be instantaneous. If the disturbance is removed after the compensatory responses have been initiated, the system may overshoot in the direction opposite to the disturbance. This overshoot will then be registered as a deviation from the set-point, and a further but opposite compensatory response will be set into motion; i.e., the system will tend to produce oscillations rather than stability.

It is emphasized that equation 4 shows that there must always be some change in the regulated variable, even when the open loop gain is high. How much the regulated variable changes depends not only on the open loop gain but also on the size of the disturbance.

If one wants to think in terms of how much disturbances are reduced, rather than in terms of the amplification of the compensatory component, then one may define error attenuation:

$$\text{Atten} = \frac{1}{1 + G} \tag{5}$$

Substituting this in equation 4:

$$d_{reg} = \text{Atten} \times \text{Dist}$$

For example, suppose the loop gain is 4, and the error attenuation is 0.2. This means that disturbances cause only ⅕ of the change they would have caused in the absence of the negative feedback component. This amount of error attenuation for a relatively low open loop gain may seem quite large. It must again be emphasized that the actual change seen depends not only on the error attenuation but also on the size of disturbance.

Disturbances are sometimes called *open loop factors*. This should not be confused with *open loop gain*.

## BODY WEIGHT AND PALATABILITY OF THE DIET

When rats are offered palatable diets, their weights stabilize at higher levels (Corbit and Stellar, 1964; Maller, 1964). When their food is made bitter with quinine, weights stabilize at lower levels (Peck, 1978). Reinstating the usual diets reverses these effects; i.e., the effects are different from the persistent obesity described in Chapter 5: in that case the high-fat diets were available for a number of months, long enough to induce fat cell hyperplasia, which may have been responsible for the maintenance of the higher defended level of body weight.

One possible explanation for reversible diet-induced changes in body weight levels is that taste alters the regulated level in some relatively direct way. Just as stimuli from cold and warm detectors in the skin alter the firing rates of thermosensitive neurones in the preoptic region, so stimuli from the mouth might adjust some CNS regulatory mechanisms for body weight. There would be no problem in calling this rheostasis, but there is little supporting evidence for such a mechanism, and a more plausible explanation exists.

Good taste might directly augment the amount eaten. In this case the closed-loop part of the system would be unaltered but left in conflict with a more powerful open-loop factor (Peck, 1976; Mrosovsky and Powley, 1977). To take a common example, suppose people at their usual weight have just eaten a large and satisfying meal. The host then appears bearing an artistic and appetizing chocolate and cream bonne bouche. Such open-loop factors might be strong enough to overcome a relatively weak regulatory defense. But the defenders need not be completely overrun. If there is a proportional control system, the more the defenders are pushed back, the more they resist. Eventually they manage to stabilize the situation but in a different position. A similar scenario takes place when a rat in a cage is presented with an array of supermarket foods; it is not surprising that it gains more weight than on laboratory chow.

A body of evidence supports the open-loop explanation of dietary obesity. Defense of the higher weight is poor. When food deprived, these rats are less prepared than controls to eat quinine-adulterated food or to work at bar press-

ing to obtain food. They regain weight after a fast at a slower rate than controls (Sclafani and Springer, 1976). Food-deprived rats and various other species (Cornish and Mrosovsky, 1965) become more active when they lack food. Presumably in natural conditions locomotion increases the chance of encountering food. In contrast, dietary obese rats do not run more in wheels when their supermarket diet is removed. Eventually, when weights have fallen to levels similar to those of rats fed chow throughout their lives, they become more active. This suggests that the dietary obese animals defend the same rather than elevated weights (Sclafani and Rendel, 1978).

The evidence to the contrary is weaker and equivocal. For instance, rats fed different diets and at different weights will still increase their intakes when in a cold environment (Peck, 1978). It is debatable whether this is a response in defense of body weight or body temperature. It is present soon after the rats are put in the cold, before appreciable weight changes occur. This contrasts with the approximately 15% weight loss needed to make rats fed a chow diet more active (Sclafani and Rendel, 1978). Moreover, the rats fed a high-fat diet in these experiments ate less, not more, and lost a little weight when first put in the cold (Peck, 1978). It is not evident that they defended their weight against this challenge. When dietary obese rats are stomach loaded with food, their voluntary intake goes down (Peck, 1978). This may indicate some defense against getting still fatter, but it provides no evidence that the higher weights of dietary obese rats are defended against challenges that would otherwise make them lose weight. The similar weight loss (~5%) required to initiate hoarding by supermarket diet and chow fed rats might be taken as suggesting that dietary obese rats defend their weights, but in this case the supermarket group was barely 30 g (~7%) heavier than the controls at the time of testing. Since they were hardly obese, hoarding behavior similar to that of controls would be expected anyway (see also Chapter 6; Winn and Herberg, 1985). Overall then, setting aside persistent obesity associated with fat cell hyperplasia, the evidence generally favors the view that palatable foods can drive rats above their set-points for body fat by overriding a regulatory system with relatively low gain.

A similar situation probably occurs as part of the syndrome of hypothalamic obesity (Sclafani and Rendel, 1978). Animals with lesions in the ventromedial hypothalamus, like those with dietary obesity, defend their elevated weights poorly (e.g., Franklin and Herberg, 1974; Ferguson and Keesey, 1975). "Although the etiologies of the dietary obesity and hypothalamic obesity syndromes differ, the net effect—the supra-set-point body weights—may be the same" (Sclafani and Springer, 1976).

While an open-loop interpretation appears satisfactory for accounting for hypothalamic and diet-induced weight gains, problems arise when it comes to applying it to weight losses on unpalatable diets. When quinine is mixed into rats' food, their weights decrease and stabilize at lower levels (Peck, 1976). Perhaps some of this effect is the result of the bitter taste itself; the increased spillage of rats on quinine diets suggests they were still hungry and looking for better food that would help them maintain body weights (Peck, 1976). But part of the effect is also caused by post-ingestional effects of quinine. Quinine sul-

fate and quinine tannate contain equal amounts of quinine base and depress body weight equally. Yet the tannate is not nearly so bitter and is preferred to the sulfate by rats given a choice (Heybach and Boyle, 1982a). Several groups have also shown that sucrose octaacetate does not reduce weight although it tastes bitter (e.g., Heybach and Boyle, 1982a). Also, administration of quinine directly into the body through implanted minipumps depresses body weight (Heybach and Boyle, 1982b). These and other considerations show that "there is more to quinine's effects on feeding than meets the taste bud" (Gunion and Peters, 1983).

The lower body weights of rats receiving quinine are nevertheless defended. Rats reduced in weight prior to being given the drug actually gain weight until they reach levels equaling those to which previously undeprived animals have fallen after receiving quinine (Kratz et al., 1978; Heybach and Boyle, 1982b). Defense of weight in terms of increased efficiency of food utilization is the same in rats fed a quinine-adulterated diet as in those fed normal chow (Boyle and Heybach, 1982). The postingestional action of quinine makes it difficult to invoke the most obvious open-loop mechanism, depression of intake by unpleasant taste, as responsible for its weight-reducing effects. At least the possibility should be considered that this substance lowers the regulated level by altering the closed-loop part of the system.

In addition to this work with rats, there is at least one experiment with people that suggests that unpalatable diets lower defended levels of weight. In this experiment, Cabanac and Rabe (1976) studied reactions to sweet taste by volunteers before and after they underwent a 3.1 kg weight loss when fed exclusively with a monotonous liquid diet. They found that negative alliesthesia persisted after the weight loss: glucose loads to the stomach decreased the pleasantness of sweet tastes as much as they did before weight loss. To appreciate this result it is useful to describe what happened when weight was reduced by comparable amounts (2.7 kg) by limiting the amount rather than the quality of the food. After the deprivation-induced weight loss, negative alliesthesia was absent: sweet tastes remained pleasant or neutral after a stomach load, indicating that food-deprived subjects were below their set-point (Cabanac et al., 1971b). The reports subjects gave of their experiences were also revealing. When food restricted, they had to fight off hunger and they dreamt of food. When on the monotonous diet, they did not have these problems.

If—as these experiments imply—merely being on a monotonous diet lowers the regulated levels and results in weight loss without hunger, then it is surprising this has not received more attention from those interested in weight loss. The reliability of these results and whether they would generalize to different types of people merits investigation. The subjects in the study with the monotonous diet were not described but had relatively normal weights (Cabanac and Rabe, 1976). When severely obese patients were able to obtain only a homogeneous liquid food from an automatic dispensing device, they lost large amounts of weight and they did so without feeling hunger (Hashim and van Itallie, 1965; Hashim, 1981). In this respect the results were the same as those of Cabanac and Rabe (1976). Normal weight subjects lost some weight when eating the bland diet, possibly partly as a result of water loss and dimin-

ished sodium intake. At least one subject lost 2 kg over the course of the experiment (Campbell et al., 1971), but in general weight loss appears to have been less than in Cabanac and Rabe's (1976) experiments with monotonous diets.

Summarizing palatability effects on weight, as with exercise-induced hyperthermia, we find complications and ambiguities. Several phenomena may be involved. For obesity that persists even when highly palatable foods are replaced by ordinary fare, elevated weights are defended (Chapter 5). In some circumstances it appears that monotonous foods can lower set-points, but confirmation and elaboration are needed. For reversible dietary obesity, most evidence accords with the view that taste and texture of food act in an open-loop manner, forcing food intake up despite an unchanged but relatively weak feedback system. Even though a rat fed on a palatable diet will return to an elevated weight after a period of deprivation, it is legitimate to question whether this is enough to say there is a set-point change, especially when different indices of defense suggest otherwise. Unless the discrepancy between the weight eventually attained on a palatable diet and the initial weight on the chow diet is causal in the weight gain, some will object to invoking set-point changes, or even to saying that it is as if the set-point had changed (Toates, 1983).

## GONADOSTAT RESETTING REVISITED

Both steroid-dependent and steroid-independent processes probably contribute to changes occurring at puberty and seasonally. The steroid-independent process can be viewed as an open-loop factor acting unrestrained by feedback. It was argued in Chapter 4 that steroid-independent changes were not, in fact, the whole story, but if that evidence is unacceptable and someone wants to take the extreme view that none of the maturational and seasonal changes are steroid-dependent, then it becomes debatable whether gonadostat resetting, operationally defined, should be included as an example of rheostasis. This is an extreme view; it may also be pointed out that, except perhaps in one case (Bittman and Goldman, 1979), experiments emphasizing steroid-independent effects have not ruled out the possible influence of adrenal steroids in castrated animals (see Schillo et al., 1988). I think the evidence for there being some steroid-dependent effect is strong enough to warrant not considering gonadostat resetting as a problem case in the same category as exercise-induced hyperthermia and dietary obesity. It has, therefore, been described previously (Chapter 4).

## CHAMPIONING THE OPEN LOOP

Limited open-loop gain, and corresponding constraints on effectiveness of error attenuation, are generally classed among the disadvantages of a negative feedback system (e.g., Houk, 1988), a price that must be paid to avoid instabilities. That is correct from an engineering point of view, *if* one wants to achieve maximum stability. But—and the point has been made repeatedly—in

the real biological world of the whole animal, with conflicts between its different homeostatic systems, and the need to anticipate seasonal shortages, and for other reasons, constancy is not always the ultimate aim. Permitting strong open-loop influences is one way to allow for, or even promote, inconstancy when it is needed. Homeostasis is a magnificent and widely applicable explanatory concept, but there is no need to let it dominate physiological thinking.

As an example, consider thermoregulation during intense activity. Despite removal of much of the heat produced by the muscles during exercise, there is still a rise in temperature. If activity is prolonged and intense, and if the avenues for heat loss are limited by warm or humid environments, then the temperature continues to rise. Eventually heat exhaustion occurs. This has been considered earlier (Chapter 2) as an example of leaving the conflict situation, the conflict being one between the muscles and the skin over blood supply. If temperature rises too much, thermal considerations assert themselves in the form of heat exhaustion and reduction of muscular heat production. Collapse occurs close to a temperature and physiological state that may be fatal. Why does collapse not intervene at less extreme temperatures and so preserve a more stable body temperature? The answer is easy to see if we return to the example of the man pursued by the lion (Chapter 2). If heat exhaustion intervened after only small increases above normothermic levels, then he would hardly have run a few hundred meters before he fell prostrate and the lion was upon him—unless, of course, the lion's activities were similarly constrained by its thermoregulatory system. Then the lion would miss his meal. Obviously evolution steps in. In fight or flight, both for predator and for prey, in circumstances where intense activity has survival value, there will be pressures to let temperature rise as much as possible before heat exhaustion intervenes. A powerful thermoregulatory system is a disadvantage if it entails heat exhaustion and collapse too readily.

Another reason for not insisting on thermal stability is the beneficial effect of higher temperatures on the work capacity of the muscles. In 1945 Asmussen and Bøje showed that, whether the warming is achieved by preliminary work or by diathermy, muscles can develop greater tension and finish a given amount of work in a shorter time. The beneficial effects of warmth on the muscles and the ability to complete work in a short time should be distinguished from the demands of prolonged submaximal exercise during endurance performance where different thermal considerations, including the value of not getting too hot, may apply (Chapter 5; Hessemer et al., 1984). But for the tasks studied by Asmussen and Bøje it is instructive to quote what these authors said about their findings. At that time the view that exercise entailed an elevation in set-point was beginning to gain ascendency. After alluding to the still earlier view that exercise hyperthermia was "a sign of failing temperature regulation, endangering the continuation of work," Asmussen and Bøje wrote: "The work of Nielsen (1938), however, threw new light on the subject by demonstrating, that—inside a wide range—the rectal temperature during exercise rises to a constant level, dependent on the rate of work, but independent of the environmental temperature." Then, after describing their findings on the beneficial effects of elevated temperature on the work capacity of the muscles, they ended their

paper with the following sentence: "The accurately regulated higher rectal temperature in work (Nielsen) allows the muscles to obtain a higher temperature during work than would otherwise be possible."

Now that we are returning to the older view that the regulated level is not elevated during exercise, does that make the effects of the higher temperatures on muscles any less beneficial? Should exercise hyperthermia really be thought of as a failure of regulation? In terms of adaptive value, the important thing is that temperature stability be relaxed somewhat under conditions of physical activity. How that is achieved is a matter of mechanisms. The difficulty that thermoregulatory physiologists have had in resolving the matter indicates that both the set-point and the load error mechanisms have at least some general similarities in outcomes. Even if the hyperthermia were entirely the result of greater heat production driving the temperature away from its set-point, the temperature does more or less stabilize at a higher value. Homeostasis does not depend on one type of mechanism only (Chapter 1), nor need rheostasis. "Nature selects for outcomes" rather than for mechanisms (Lehrman, 1970). It may, therefore, be argued that higher temperatures during exercise should qualify as rheostasis.

Similar arguments apply to body weight changes as a function of the diet. There may be some survival value in not maintaining one's fat reserves at as high a level, and in not eating as much, when the food tastes terrible. It is by no means certain yet that regulated levels cannot change in reaction to different diets, but on balance it seems that open-loop factors are more important. In either case weights stabilize at different levels and there is some defense of these levels. The set-point, in the descriptive sense, changes.

## EVALUATION OF OPPOSING VIEWPOINTS: MATTERS OF PREFERENCE AND TERMINOLOGY

Previous sections have presented arguments both for and against including phenomena such as exercise-induced hyperthermia and palatability effects on body weight as examples of rheostasis. Which viewpoint is adopted is a matter of preference more than anything else. But it should be noted how the terminology used in discussing these matters is often enriched with value judgments. For instance, the "as if" use of the term *set-point* has been designated the "metaphorical" use by Toates (1983); this conjures up mental images of a land beyond the realm of science. Others have preferred a less colored but less loaded label, simply the "descriptive" use of the term *set-point* (Mrosovsky and Powley, 1977). The term *open-loop factor* is also more neutral than the term *disturbance*. Again, limited error attenuation is often considered as a disadvantage in a negative feedback system because *error*—the most value-laden term of all—is necessarily bad. But when biologists borrow concepts from engineering and control systems theory, they are not obliged to accept the prevailing attitudes in these other disciplines. To some, deviation from a constant value is an error: to others, it may be a demonstration of flexibility.

Perhaps for a biologist, neutral terminology is preferable if it promotes

recognition of the validity both of the control systems approach and of the descriptive functional approach to rheostasis. And if individual preference is to determine which view is acceptable, at least it should be noted what adopting each of these views is liable to entail. A strict control systems approach may lead to classifying as disturbance, or as noise, factors and changes that have important functions. It may lead to dismissing some phenomena as possible examples of rheostasis because, as is so often the case, their underlying mechanism is not yet known. But the descriptive approach could lead to so many phenomena being classed as examples of rheostasis that the concept would become too elastic to be satisfactory. Temporary and rapidly overcome perturbations of homeostatically controlled variables have to be excluded.

In this book, a scratching only at the rudiments of the subject, a compromise has been adopted. In the examples of rheostasis included in Chapters 4, 5, and 6, there seem to be at least some indications that the body is actively promoting change rather than trying to defend a steady level. Examples of change where there are some very obvious candidates for open-loop factors, such as in exercise hyperthermia and the palatability effects on weight, have been set apart in this chapter. The problem is flagged but not solved. But whether such cases qualify as showing rheostasis or not, one thing is absolutely certain: These are *not* examples of homeostasis. They are examples of something other than conventional successful homeostasis. But they do not necessarily represent failure. They are a part of the physiology of change whose mechanisms and value need elucidating as much as does the maintenance of stability.

## DIFFERENT MECHANISMS OF RELAXING CONSTANCY

This treatise has concentrated on a particular type of change, that where the regulated level changes but the effectiveness of regulation remains the same or is still manifest to a high degree. The preference has been for cases where, even if the data are not always adequate to be sure, it appears that the line relating the magnitude of the corrective response to the actual level of the regulated variable shifts to the right or the left. It may be debated whether this type of change in a regulatory system should be given more emphasis than other types of change. The function relating response strength to a regulated variable may change in ways other than shifting sideways. For instance, the slope of the function may decrease. This sometimes occurs with thermal responsiveness during fever, in addition to the threshold shifts (Székely, 1984). Changing the slope is also a way of introducing flexibility because with a proportional control system when there is a load, then there always is some discrepancy between the actual and the set value of the regulated variable. If the proportionality constant is decreased (another way of saying that the slope is decreased), then these discrepancies become greater. Regulation will not be as precise as with a higher slope.

Yet another type of change in the relationship between a response and the actual value of the regulated variable occurs when there is an increase in the

scatter of the points producing the function. With greater variability the response is less predictable and on some occasions does not occur at all. Combining these last two types of change, the slope of the function can decline and the scatter increase so much that regulation disappears. From a teleological point of view, if defense of a particular level of a variable needs to be relaxed or abandoned, there are ways of doing this other than maintaining the same effectiveness of regulation but shifting the threshold. It may be artificial to focus too much on threshold changes. These are not just abstract considerations because there are indeed some remarkable instances of this type of weakening, and in extreme cases loss, of homeostasis. The next sections provide some examples.

## PARADOXICAL SLEEP: LOSS OF THERMAL HOMEOSTASIS

During paradoxical (rapid eye movement, REM) sleep, shivering, panting, sweating, and vasomotor responses are virtually absent, and neurones in the preoptic region become much less thermosensitive. "This sleep stage in several species is characterized by a dramatic impairment of homeostastic regulation" (Parmeggiani, 1987). One may wonder, in the light of other examples where lack of constancy has some value, whether the word *impairment* has the correct coloring for a full appreciation of the phenomenon. Perhaps there is some useful function in the shut-down of thermal homeostasis in paradoxical sleep. In fact, as Parmeggiani (1987) points out, there are limits on how much temperature can actually change as a result of bouts of paradoxical sleep. First, sleep time is greatest at thermoneutrality; at progressively higher or lower ambient temperatures more time is spent awake. Second, the likelihood that a bout of paradoxical sleep will follow one of slow-wave sleep depends on body temperature. Outside a narrow range of hypothalamic temperatures, paradoxical sleep seldom follows slow-wave sleep.

## LOSS OF $CO_2$ REGULATION DURING REM SLEEP

During REM sleep, especially during the particular times in REM when twitching and rapid eye movements are actually present (phasic REM), there is a loss of the normal relationship between ventilation rate and $CO_2$ levels. In tests with dogs, when the loop between respiratory activity and $CO_2$ levels was broken by having the animals rebreathe from a bag of air, instead of the minute volume increasing linearly with $P_{CO_2}$, as it did in slow-wave sleep, there was only a weak relationship between these variables (Fig. 7–4; Sullivan et al., 1979). In these experiments the air to be breathed started off with percentages of oxygen high enough to keep the dogs hyperoxic throughout; lack of oxygen was therefore not a factor.

Minute volume in REM was generally higher than it was in slow-wave sleep at the same $P_{CO_2}$. The scatter of these points therefore does not neces-

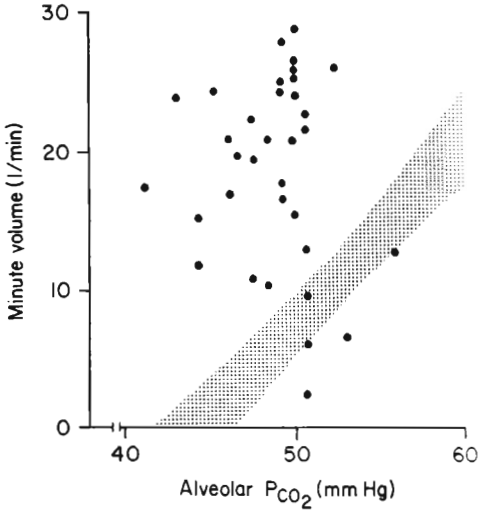



**Figure 7–4.** Respiratory response of dogs to various $CO_2$ pressures while rebreathing from the same air. Dots show responses during REM sleep; shaded area shows 95% confidence limits for data obtained during slow-wave sleep (adapted from Sullivan et al., 1979, *J. Appl. Physiol.* **47**, p. 1306).

sarily in itself mean that the system is unresponsive to high $CO_2$ levels. It suggests, rather, that most of the time in REM neural inputs maintain respiration and $CO_2$ levels above a level where $CO_2$ becomes an important drive to the respiratory center (Sullivan, 1980). Nevertheless, there does appear to be an abandonment of $CO_2$ homeostasis in REM. There are a few points in Figure 7–4 where breathing rates were lower than in slow-wave sleep at the same $P_{CO_2}$. Also there were occasions associated with swallowing and licking movements in REM, when breathing was interrupted altogether, despite hypercapnia. However, there is some safety net in that, even though the ventilatory response to $CO_2$ fails in REM, the arousal response is still present, though it requires higher levels of $CO_2$ to trigger it than are needed during slow-wave sleep (Phillipson et al., 1977).

Why should both temperature and $CO_2$ homeostasis be jettisoned in REM? No convincing suggestions have been made. According to Shapiro et al. (1974), "it would seem, active sleep and precise thermoregulation are mutually exclusive," but they offer no suggestion as to why this should be. The solution to this tantalizing problem will surely be instructive either about homeostasis or about the function of REM. Perhaps there are some undetected conflicts between REM and the maintenance of homeostasis. In the related case of loss of $CO_2$ homeostasis during speech, conflict is implicated.

## $CO_2$ DURING SPEECH

The respiratory apparatus serves speech as well as breathing. It is not surprising therefore that the regulation of $CO_2$ levels changes when someone is talking. Subjects breathing air containing 3% $CO_2$ while they are speaking allow their alveolar $CO_2$ pressures to rise higher than when they are silent (Bunn and Mead, 1971). It has been calculated that, without this change during speech,

hypercapnia would result in an increase in tidal volume of sufficient magnitude to prevent more than the utterance of isolated syllables; speech would resemble that of someone exercising heavily (Phillipson et al., 1978). Using the rebreathing method, it has been shown that during speech a combination of decreased slope of the response to hypercapnia and of increased scatter of the points virtually eliminates the regulation of $CO_2$ at normal levels (Fig. 7–5). Even during inspiration, when sound production does not actually take place, the airflow is relatively unaffected by $CO_2$ levels. However, within 30 seconds of stopping talking there is an abrupt reestablishment of the ventilatory response to hypercapnia (Phillipson et al., 1978).

Of particular interest is that the subjects in these experiments felt no distress or discomfort. This contrasts with the effort required to hold one's breath. Homeostasis can be overridden by will power or persuasion. Simply paying men \$0.02–0.04 for each minute they remain in a cold room, and signaling their gains prominently on a digital display, is sufficient to keep them there despite scanty dress, intense shivering, and drops in skin temperature (Johnson and Cabanac, 1983). Hunger strikes or experiments where people gain (Sims and Horten, 1968) or lose weight (Keys et al., 1950) are further illustrations of the limited power of homeostasis. But overriding homeostasis voluntarily requires effort and is not comfortable. It is different from the automatic relaxing of $CO_2$ regulation that occurs during speech.

Possibly changes in the slope of compensatory responses, and in the scatter of points producing these slopes, should have been considered at greater length. The few examples given in this chapter at least provide some recognition that defense of a particular level of a regulated variable can be abandoned by ways other than threshold shifts.

## ADAPTIVE VALUE OF RHEOSTASIS: LEVELS OF EXPLANATION

The exposition of examples of rheostasis in this book has frequently included suggestions about adaptive value of rheostasis. This may be enriching for those who enjoy moving freely between causal and functional levels of analysis, and

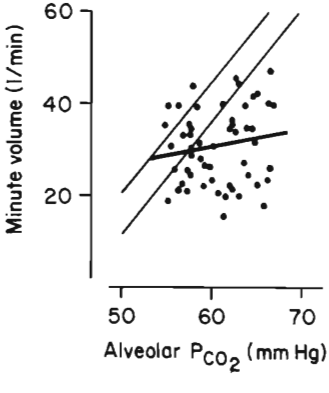



**Figure 7–5.** Respiratory response to alveolar $P_{CO_2}$ during speech and silence. Dots and heavy line show data points and regression for a person speaking continuously while rebreathing from the same air. The area between the thin diagonal lines shows the 95% confidence limits for the same subject during quiet rebreathing (adapted from Phillipson et al., 1978).

it may even suggest possible experiments. More mechanistically minded physiologists may prefer to ignore evolutionary considerations and get on with their experiments. Skeptics about adaptationist explanations may be provoked to attack: speculations about survival value are hard to test, often facile, and can be replaced by equally plausible alternatives. If the wolf grew fur on its foot pad in the winter, the conflict between preventing frostbite and losing heat from its extremities would not be so acute, and rheostasis of temperature in the foot would not be as necessary. If the cichlid fishes, which as a group are inventive enough to have come up with some amazing adaptations, had devised a way of bypassing the young as they take in food, they would not need to lose weight during mouthbrooding. If male waterfowl helped out a little more during incubation, the conflict between feeding and keeping the eggs warm and protected would not arise; lowering of body weight set-points would not be needed.

Such points are not disputed, but they are directed at a different level of explanation than the speculations about the adaptive value made in this book. Indeed, some Arctic animals, the wolverine for example, do have a furry underside to their foot in the winter (Henshaw, 1978, 1986); the ability to regulate the foot-pad temperature at just above 0°C is still present, but this mechanism need not be brought into action as much. Some fish are successful without mouthbrooding, and the males of many avian species share the task of incubation. Yet for the wolf, for some reason, be it genetic constraints, evolutionary inertia or because a glabrous foot has some undiscerned advantages, hair in this part of the body is lacking. Given this situation, local thermal rheostasis is of especial value. Given that some fish are mouthbrooders and that some waterfowl are single-sex incubators, lowering of defended levels of body weight is adaptive for them. Rheostasis has value as a way out of predicaments. That is not the same as denying there might be other ways out of such predicaments or of asserting that incorporating rheostasis into homeostatic systems is advantageous in itself. Given that the pieces on the chess board are in particular positions, one helpful move may be to sacrifice the knight. But if the game were started all over again, that move might be of no value. If one had been building "survival machines" from scratch, the optimal design would not necessarily have included rheostasis.

## PATHOLOGICAL RHEOSTASIS

There are often good reasons for altering the defended level of a variable, but this does not mean that rheostasis is always adaptive. When it comes to changes common in old age, it may be especially appropriate to beware of overenthusiasm about the survival value of rheostasis. At the same time, given the numerous other situations in which rheostasis contributes to the overall maintenance of the organism, it may be unwise to peremptorily dismiss the possibility of an adaptive side to changes in aging. For instance, Cabanac and Russek (1982) have suggested that greater adiposity helps older animals, those that are less capable of hunting and competing with conspecifics, to survive periods of shortage. This may not be a particularly compelling argument, but neither

is it particularly objectionable. When it comes to hyperglycemia in diabetes and to hypertension, Cabanac and Russek's (1982) speculations about adaptive value may be more startling. Hyperglycemia is a valuable reaction that enables the muscles and other tissues to receive adequate glucose in the face of insulin resistance. There may be something in these views. The real culprit may be the insulin resistance, not the hyperglycemia.

By analogy, hypertension may compensate for deficient circulation. Suppose that for some reason the brain is not getting enough oxygen to carry out its coordinating functions, or the kidney is not receiving adequate blood supply to perform its excretory functions, then there is some value in raising the blood pressure. Hypertension in these cases is not so much a disease in itself as a compensatory reaction produced by important organs to maintain important functions. For these reasons, rightly or wrongly, some physicians have been cautious about reducing blood pressure in patients with cerebral vascular disease. Following a stroke there may be impaired autoregulation; further reduction of blood pressure and cerebral blood flow could make things still worse. Even those who feel that the dangers of high blood pressure outweigh these considerations—and who have found that in their experience reducing pressure in hypertensive stroke patients does not increase the risk of further stroke—caution against lowering blood pressure too rapidly (Gottstein and Seel, 1977). Moreover, after treatment with antihypertensive agents, there is a J-shaped relationship between deaths from myocardial infarction and blood pressure in patients with ischemic heart disease; lowering diastolic pressure below 85 mm Hg is associated with increased mortality (Cruickshank et al., 1987).

All the same, statements about adaptive value in such cases require qualifying when there is a danger of hemorrhage and other pathology. There is obviously a pathological side to hypertension. The heart has to work harder, the blood vessels become sclerotic and weaker, the danger of stroke and other hemorrhage increases. Rheostasis may indeed be adaptive in many circumstances—a view this book has indulgently promoted—but in other cases it may do as much harm as good. There are two obvious ways in which this could happen. First, rheostasis might simply be too great in extent. Fever helps combat infection, but too high a fever may not be beneficial (Chapter 5). Likewise, too high blood pressure becomes deleterious (Chapter 5). Programmed rheostasis also can be carried too far. Occasionally incubating geese starve to death on their nests (Chapter 4). Second, there may well be examples of a purely pathological rheostasis, that is rheostasis occurring at inappropriate times or in reaction to inappropriate stimuli. Any physiological mechanism, however valuable it is on average, is likely to have a darker side that manifests itself occasionally in pathology.

## SPECIES DIFFERENCES AND EXCEPTIONS

Chapters 4–6 have shown that the body does not always attempt to maintain the internal milieu in a unique stable state. Rheostasis is common and occurs in a variety of circumstances and regulatory systems. The aim of this review has been to describe findings that exemplify rheostasis rather than to cover

studies that do not show this phenomenon. That is beyond the scope of this book, but by way of balance, it may be appropriate to mention some experiments in which rheostasis was not found. When similar studies in apparently similar circumstances have produced evidence of rheostasis, an absence of rheostasis might seem surprising and be noteworthy.

For example, among the ectotherms, administration of bacteria, endotoxins, or prostaglandins has been found to produce fever in numerous species of reptiles, amphibians, fish, and arthropods (see reviews in Boorstein and Ewald, 1987; McClain et al., 1988), but fever has not been detected in similar work with at least four reptiles (Laburn et al., 1981; Zurovsky et al., 1987a, 1987b), one fish (Marx et al., 1984) and one mollusc (Cabanac and Rossetti, 1987).

Continuous thermoregulation during the hibernating state has been demonstrated in ground squirrels and marmots but appears weak or absent in chipmunks (Pivorun, 1986).

Seasonal changes on gonadostat setting occur in a variety of species, yet in the snowshoe hare, *Lepus americanus*, castration during months when the gonads are regressed does not result in increased output of gonadotropins (Davis and Meyer, 1973), suggesting that the control system is turned off rather than turned down. According to Goodman and Karsch (1981), there is a spectrum of species ranging from those where photoperiod produces seasonal breeding mainly indirectly by altering the sensitivity to steroid feedback to species where the main effects of photoperiod are independent of steroid feedback. The snowshoe hare is presumably on the latter end of this spectrum. Even within species there may be differences. In females of some strains of hamster *(Mesocricetus auratus)*, when daylength is short hypothalamic sensitivity to steroid feedback does not seem to increase (Hauser and Benson, 1987).

Obviously, careful comparison of methodological details between studies with different outcomes should be undertaken, especially when there is evidence for rheostasis in a variety of species and circumstances, as is the case with fever. Negative results with pathogens and pyrogens may depend on the doses used or on how long the fever takes to develop or on how long it lasts. Ideally, different species should be studied by the same investigator with the same methods. Pathogenicity of the particular bacteria for the host species needs to be demonstrable. However, even if species differences in the occurrence of fever were firmly established, they would not invalidate the concept of thermal rheostasis during infection; they would merely define the limits of its applicability. Comparisons between species in different niches and with different life history strategies may also be useful in illuminating the adaptive value of some of the more puzzling alterations in regulatory levels.

## SUMMARY

Prolonged application of an open loop factor produces the impression that a variable is being regulated at a different level. It may look as if a set-point has shifted, even when the closed negative feedback loop remains unaltered. Whether such instances qualify as rheostasis may depend on how much im-

portance is attached to outcomes and how much to mechanisms. If mechanistic criteria for rheostasis are demanded, then many of the examples in this book become only candidate examples because their underlying mechanisms are still poorly understood.

Whether closed- or open-loop mechanisms predominate, the effect and the function is to allow for change rather than to maintain stability. Yielding to an open-loop factor can be viewed not simply as a case of load error but also as a way of introducing flexibility.

A different way of relaxing defense of a particular value of a variable is to weaken the effectiveness of regulation. This occurs when there is a decrease in the slope of the line relating the strength of a compensatory response to the actual value of a regulated variable and when there is an increase in the scatter of points producing the line.

Rheostasis of particular variables in particular situations is often adaptive. Rheostasis in itself may or may not have survival value. Like many other physiological phenomena, rheostasis can become pathological if carried too far.

## PREVIEW

The final chapter in this book provides a brief recapitulation and then asks if there is a place for integrative physiology at the molecular banquet.

# 8

# Molecular and Integrative Biology

## THE PHYSIOLOGY OF CHANGE

The body does not always seek constancy in its internal environment. It does not always react in ways that prevent change; sometimes physiological mechanisms actively promote change. This is no new revelation. The scientific literature already contains numerous explanations couched in terms of changing of set-points. One may read of the resetting of baroreceptors, osmostats, chemostats, and alphastats. Adjustment to thermostats, gonadostats, mechanostats, and lipostats have already been proposed. Some name is needed to recognize the generality of these phenomena. *Rheostasis* is a convenient term for designating change in regulated levels.

What qualifies as an example of rheostasis depends on how extensive or rigid are the criteria adopted and whether the preference is for errors of commission or errors of omission when information is lacking. Table 8–1 lists examples discussed in this book, dividing them into those for which the evidence for their being a defense of a different level of a variable seems fairly persuasive and those for which little more than a few suggestive hints and speculations about rheostasis exist. At the bottom come cases where obvious open-loop factors are present. This classification is provisional, arbitrary, and subjective. Some of the examples may perhaps not be justified and others could doubtless have been included. Table 8–1 is presented just by way of a recapitulation of the phenomena discussed in previous chapters and as a reminder that, whatever one may think of particular cases, rheostasis is not confined to a few esoteric difficulties encountered by atypical species. On the contrary, it contributes to major and common themes of life: maturation, the challenge of the seasons, survival and breeding, the care of the young, feeding, and the alternation of day and night. The subject merits study—but how?

**Table 8.1.** Summary of Examples of Change Discussed in This Book*

| *Programmed* | *Reactive* | *Second Order* |
|---|---|---|
| CATEGORY 1 | | |
| Incubation weight loss | Infection: fever | Irradiation: growth trajectories |
| Seasonal weight changes: hibernation | Infection: cryexia | Brain lesions: growth/fattening rates |
| Seasonal weight changes: premigration | Psychogenic fever | Precocious and delayed puberty |
| Seasonal weight changes: other | Paraplegia: thermal set-point | Circadian cycle amplitudes |
| Estrous cycle: weight | Skin temperature: thermal set-point | |
| Menstrual cycle: temperature | Undernutrition: gonadostat resetting | |
| Estrous cycle: gonadostat resetting | Undernutrition: temperature and torpor | |
| Seasonal cycles: gonadostat resetting | Undernutrition: thyrostat resetting | |
| Puberty: gonadostat resetting | Undernutrition: glucocorticoid levels | |
| Aging: gonadostat resetting | High-fat diet: persistent obesity | |
| Lactation: elevated temperature | Dehydration: elevated temperature | |
| Pregnancy: osmostat resetting | Inappropriate osmostat resetting | |
| Pregnancy: $CO_2$ chemostat | Hypovolemia: osmostat resetting | |
| Hibernation: lowered temperature | Blood pressure in hypertension | |
| Hibernation: alphastat resetting | Acute baroreceptor resetting | |
| Slow-wave sleep: lowered temperature | Heat stress: thermal set-point | |
| Slow-wave sleep: $CO_2$ chemostat | Physical training: thermal set-point | |
| Circadian cycles: temperature | Local thermal regulation | |
| Circadian cycles: glucocorticoid levels | High altitude: $CO_2$ chemostat | |
| Reproductive frenzy: glucocorticoid levels | Hypoxia: thermal set-point | |
| | Low-salt diets: $CO_2$ chemostat | |
| CATEGORY 2 | | |
| Pre-egglaying: calcium stores | Infection: weight loss | |
| Pregnancy: calcium stores | Shock: hypothermia | |
| Menopause: mechanostat change | Anorexia nervosa: temperature | |
| Antler growth: cyclical osteoporosis | Blood pressure: effects on temperature | |
| Incubation: egg cooling | Temperature: effects on blood pressure | |
| | Scrotal warming: body temperature | |
| CATEGORY 3 | | |
| | Exercise: hyperthermia | |
| | Diet-induced weight changes | |

*See Chapters 4, 5, and 6 for details and species. In Category 1 are cases where there is some evidence for a change in regulated level. Category 2 comprises the more speculative cases. Category 3 contains examples where there are obvious open-loop factors that might be responsible for the changes.

## MOLECULAR AND REDUCTIONIST APPROACHES

Once a regulatory system exists, it should be a relatively simple task for evolution to modify its setting by adjusting the strength of one of its components. For example, simply a change in the number or affinity of receptors for a feedback substance could produce a shift in regulated level. Small quantitative modulations in an existing system could be linked to biological clocks and programmed temporally. Increased transcription of a single substance might be sufficient to produce rheostasis. How could such changes be tracked down?

It would help greatly to start with information on the site of the changes producing rheostasis. For example, suppose it were known that modulation of activity in a particular area of the brain is responsible for a shift in the regulated level of a variable, then one could search for correlated phenomena in that area. Perhaps a unique mRNA or great quantities of a particular mRNA would be found. Antibodies to the corresponding proteins could then be injected to narrow down the site of action to particular cell types or receptors. However, to discover a unique mRNA would probably require comparing a cDNA library for a particular brain area to that for some control site. This could be very laborious. It would also require having a good idea in the first place of where in the brain to look for different mRNAs.

For an initial crude localization, lesion and stimulation methods still have their place. The realization that the preoptic area of the hypothalamus was important in thermoregulation stemmed in part from experiments involving lesions and local thermal stimulation. Of course, "localization" experiments of this kind must be interpreted cautiously. Presumably the preoptic region plays some role in thermal rheostasis, but other systems may be involved—for instance, in the case of fever, cytokines from the white blood cells. However, finding any manipulation at all that knocks out rheostasis of a regulated variable would at least give one a starting point, a thread to trace. The ideal would be a manipulation that eliminates rheostasis but leaves the ability to regulate intact. The lesion approach does not always yield answers easily. For example, attempts to eliminate cyclical changes in body weight in hibernators have been failures. The manipulations tried so far include vagotomy, castration, and pinealectomy, lesions of the ventromedial hypothalamic nuclei, lateral hypothalamus, paraventricular nuclei, suprachiasmatic nuclei, ascending noradrenergic bundles, and olfactory bulbs (see Zucker and Dark, 1986; Mrosovsky, 1985; Powley and Fox, 1986). In all these cases, programmed changes in body weight continued.

A different strategy for localizing the physiological mechanisms that underlie rheostasis would be to put away the electrodes and stimulators and take a correlational approach. Species that exhibit changes in regulated levels are naturally occurring preparations making their own manipulations. Instead of lesioning and stimulating particular brain areas and studying the effects, one may let the animals make their own manipulations and then try to discover where and what these are. Perhaps sufficiently salient and detectable changes exist; perhaps combinations of manipulative and correlational methods will be the most successful. Presumably, in some way or another, either by stumbling

around or by inspired insight, sufficient knowledge about the location of changes producing rheostasis eventually will be obtained. It would then become worthwhile to undertake systematic work on RNAs in particular areas.

A different approach would be to find a genetic marker in a strain of animals with an elevated set-point for a variable. If one could also find a probe for a closely linked site—an obstacle in genetically unstudied species—then it might be possible to locate the gene involved in the elevated set-point. Again, implicit in this general approach is the assumption that the adjustment of the set-point is controlled in a relatively simple way by products coded for by only one or a few genes. This is not perhaps unrealistically optimistic. It is a matter of modulating an existing system, not creating a new one. The role of the *period (per)* gene in biological rhythms of fruit flies *(Drosophila)* provides an analogy.

The *per* gene is sometimes referred to as a clock gene. In fact, what it does is to control the periodicity of circadian rhythms: mutations of the wild type ($per^+$) give rise to strains with longer ($per^l$) or shorter ($per^s$) cycles. Another mutation at the same allele lacks a circadian rhythm ($per^0$). There is no strong evidence that the *per* gene is responsible for the creation of circadian clocks. A variety of points are more consistent with the view that its main role is controlling the speed of the clock. First, the amount of transcription of *per* product is important. When rhythmicity is restored to arrhythmic ($per^-$) *Drosophila* by inserting exogenous *per* locus DNA, the frequency of the rhythm obtained varies greatly but correlates with the amount of *per* RNA produced. The variation in *per* RNA titer among different transformed strains presumably depends on the exact position of the inserted *per* gene, since location within the genome affects transcription rate (Baylies et al., 1987). Second, while expression of *per* gene products is important for the expression of biological rhythms, and for the periodicity of those rhythms, it is not essential for the development of the pacemaker mechanisms in the first place. This has been shown by controlling the expression of the *per* gene coding region by fusing it to a heat shock promoter (Ewer et al., 1988). At high temperatures there is expression of the *per* gene but at low temperatures there is little or no expression. The *per* gene, with its heat shock switch, is then inserted into the arrhythmic ($per^0$) strain. This restores rhythmicity in the right temperature conditions. It does not matter if heat is not applied until after development is completed; rhythmicity still appears when the flies become warm. "The rapidity with which rhythms can be turned on or off . . . seems to argue that *per* regulates the ongoing operations of oscillator functions, as opposed to being involved in the construction of the fly's circadian pacemaker" (Ewer et al., 1988).

A tentative idea about how *per* might influence periodicity is beginning to emerge. The *per* locus codes for a proteoglycan (Reddy et al., 1986). These proteins are important in the extracellular matrix (but could have other roles also; see Hall and Rosbash, 1988). Possibly, then, the periodicity of circadian rhythms in multicellular organisms depends on interactions between different cells. The demonstration that *per* enhances spread of dyes across the gap junctions in salivary glands of *Drosophila* suggests a general role in intercellular interactions, mediated through effects on the extracellular matrix (Bargiello et al., 1987).

Any interpretation of the new and rapidly growing findings about the molecular biology of rhythmicity could turn out to be premature. At present it appears that the effect of the *per* gene product on clock speed is a quantitative modulation of another mechanism. I am optimistic that, for at least some cases of rheostasis, the mechanisms will turn out to be relatively simple, perhaps of a purely quantitative nature. Finding these mechanisms will provide important therapeutic tools, enabling the clinician to alter the plans of a hostile regulatory system at its command post rather than doing battle with its effector armies in the periphery.

However, while the ability to manipulate set-points might perhaps—with luck, and with the aid of modern techniques—turn out to be relatively straightforward, that would remain far short of providing an understanding of homeostasis itself, just as the ability to alter the periodicity of rhythms in fruit flies has not explained how their clocks work. To fully understand the machinery underlying homeostasis and the interactions between homeostatic systems may also require analysis at levels not adequately encompassed in molecular biology.

## INTEGRATIVE PHYSIOLOGY

The search for substances and molecular bases for rheostasis, the reductionist approach, may be only half, perhaps the easy half, of what needs to be undertaken. There may also be value in continuing to study rheostasis with concepts appropriate to understanding and conceptualizing events at levels removed from that of molecular biology. Complex processes may emerge from interactions in the whole organism that have no obvious counterpart in the genes. Differentiation of embryonic tissue into the adult form provides an illuminating example.

Although development usually proceeds in an orderly, predictable way, there is no need to assume that the genes contain developmental programs. For a phenomenon to be called programmatic, "it is a necessary condition that in addition to the phenomenon itself, there exists a second thing, the 'program,' whose structure is isomorphic with, i.e., can be brought into one-to-one correspondence with, the phenomenon" (Stent, 1982). An alternative way for regularity to arise in a series of events is for a particular stage of development to create a situation that promotes the move to the subsequent stage.

> To illustrate the difference between programmatic specification and stochastic history as alternative accounts of regular phenomena, we may consider the establishment of ecological communities upon colonization of islands, or growth of secondary forests. Both of these examples are regular phenomena in the sense that a more or less predictable ecological structure arises via a stereotypic pattern of intermediate steps, in which the relative abundance of various types of flora and fauna follow a well-defined sequence. The regularity of these phenomena is obviously not the consequence of an ecological program encoded in the genome of the participating taxa. Rather it arises via a historical cascade of complex stochastic interactions between various biota (in which genes play an important role, of course) and the world as it is. (Stent, 1982)

Knowledge of the genome is not enough for understanding such historical cascades. Because of the sheer number of components and interactions, study of historical interactions in the course of development is a daunting prospect. However, if concepts and experimentation at the appropriate level of analysis can be found, perhaps the task may be simplified. For instance, Larsen and McLaughlin (1987) believe that for morphogenesis, the appropriate level of analysis is the cellular level. There may be a relatively limited number of cellular processes, a small "morphogenetic alphabet" that determines the shape of a particular tissue and when it assumes that shape. The letters in this alphabet are cell division, cell growth, cell shape, cell change, cell movement, cell death, and cell membrane and extracellular matrix production. A change in one of these processes, as exemplified in mutant fruit flies, can have dramatic consequences for the development of an organ. Which organ is affected and when it is affected depends on the timing of these changes. Environmental events such as temperature and nutrition also influence timing. "The gene cannot 'master-mind' morphogenesis since it is only a part of an interactive epigenetic system, influenced by, as well as influencing, the cell and tissue in which it resides" (Larsen and McLaughlin, 1987).

Likewise, for homeostasis, the organizational and integrative aspects of physiological functioning may not be apparent in the DNA sequences. For homeostasis to be comprehensible, analysis must take place at different levels. One appropriate level is that of organ systems and hormonal and neural signals between those systems. The simplifying concepts are those from control systems theory. If this approach is valid, then a study of principles governing the switch between different effectors, of open and closed loops, of conflict between different regulatory systems, and in what sense set-points exist and can change, of homeostasis and rheostasis in general, is not just the last gasp of a superseded era in biology. It is a part of an integrative physiology that will be coming back into its own to tackle these problems, or to replace them by formulations and concepts better applicable to interactions at levels where a knowledge of all nucleotide sequences in the world would still leave darkness. If there is no biochemical homunculus to be found in the genes for the complexities of the whole organism, then integrative physiology must come back into its own, indeed will have to be greatly developed and elaborated if we are ever to make sense of ourselves.

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