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

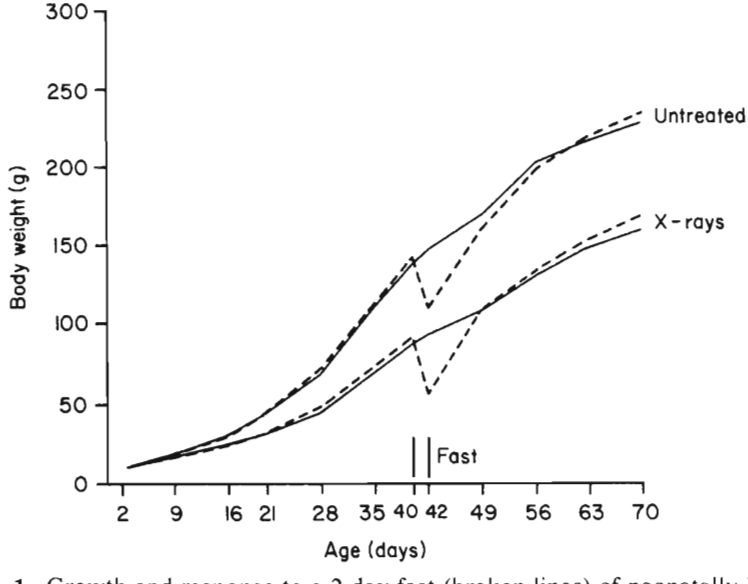

Figure 6–1. Growth and response to a 2-day fast (broken lines) of neonatally X-irradiated rats and untreated controls (adapted from Mosier et al., 1983, *Growth* **47,** p. 18).

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

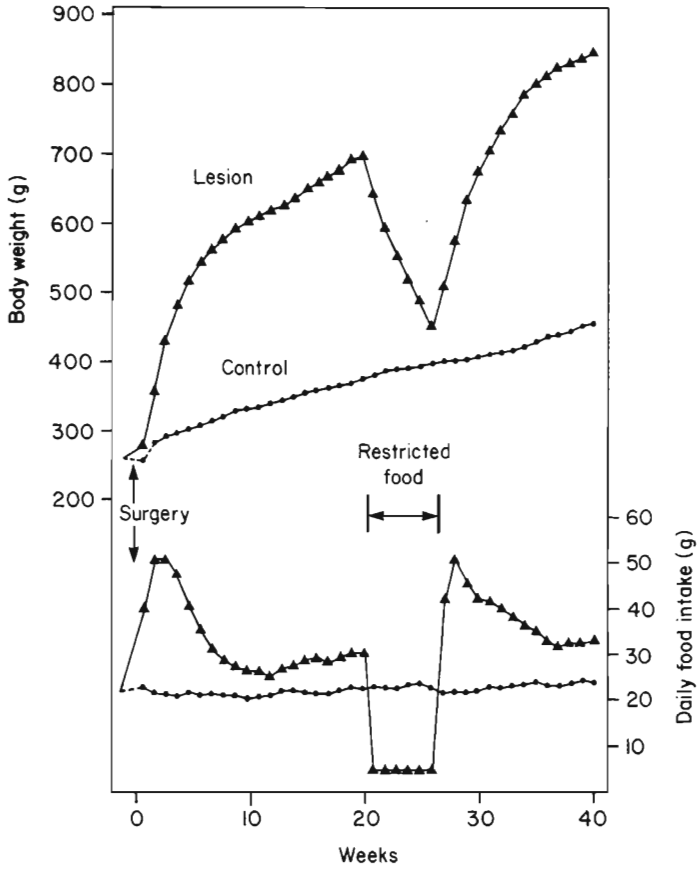

Figure 6–2. Body weights and food intakes of rats with ventromedial hypothalamic lesions and of sham-operated controls. (Adapted from Hallonquist and Brades, 1984, Ventromedial hypothalamic lesions in rats: gradual elevation of body weight set-point. *Physiol. Behav.* **33,** p. 832. Copyright 1984,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