nitrogenous compounds, such as urea, trimethylamine oxide, betaine, and sarcosine, or carbohydrates such as glycerol, sorbitol, and mannitol. The total intracellular ionic content is fairly low and constant. Where there are large increases of intracellular solute concentration, it is typically the concentration of organic molecules that varies. The ionic environment of animal cells is always dominated by K^+, rather than Na^+, and generally has a low Cl^- concentration. The intracellular pH is always close to neutrality. This basic pattern of high organic content, low ionic content, high K^+ relative to Na^+, low Cl^-, and neutral pH is consistent for protozoans and all animals, from freshwater to the most advanced terrestrial animals, such as mammals and insects. It therefore seems safe to conclude that the internal environment of the unicellular organisms that evolved about a billion years ago would have been similar in basic composition to that of extant protozoans and animals.

Homeostasis and Regulation

The maintenance of an intracellular environment that differs from the extracellular space and the external environment is, as we have seen, a characteristic of most animals. The compositions of the intracellular and extracellular fluids are often maintained constant, or at least relatively constant, even in the face of fluctuating external conditions. Such a constancy of conditions is called **homeostasis**, or "la fixité du milieu intérieur" as described by Claude Bernard. The term, homeostasis, was originally coined to describe the stability of conditions of mammalian body fluids. Referring to the extracellular fluid environment of humans, Cannon (1929) stated that

> This "internal environment" as Claude Bernard called it, has developed as organisms have developed; and with it there have evolved remarkable physiologic devices which operate to keep it constant. . . . So long as this personal, individual sack of salty water, in which each one of us lives and moves and has his being, is protected from change, we are freed from serious peril. I have suggested that the stable state of the fluid matrix be given the name of homeostasis.

Examples of homeostasis include constancy of body temperature in mammals and birds, constancy of blood gases (pO_2 and pCO_2) in body fluids of many animals, blood pressure in animals with circulatory systems, and body water content in most animals. Such examples of homeostasis are more apparent, and operate more precisely, in higher animals (such as mammals and birds, but also in certain insects and mollusks), compared with lower invertebrates that are characterized by less constant internal conditions and homeostasis of fewer physical and chemical variables.

Homeostasis, or constancy, of physiological conditions should not be confused with the concept of regulation. Certain aspects of the internal environment can be constant, even in the total absence of a regulatory mechanism; and regulation of a variable does not necessarily imply constancy. For example, the body temperature of an icefish, which lives in the ice-cold antarctic seawaters, is $-1.9°$ C and might not vary over a year by more than 1° C, a variation less than that of human body temperature over a 24 hour period! The constancy of the body temperature of an icefish is a consequence of its living in water that has an extremely stable temperature of $-1.9°$ C, since the fish's body temperature is virtually identical to the water temperature. We should not conclude that the icefish has a better thermoregulatory system than a mammal! Similarly, the ionic composition of the extracellular fluids of echinoderms is quite constant, but this does not imply great powers of regulation. In fact, the ionic composition of the extracellular fluids is nearly identical to that of seawater. Again, constancy or homeostasis is an attribute of the external environment, not of the animal. Changing the temperature of the water in which the icefish lives, or changing the ionic composition of seawater surrounding an echinoderm, will invariably alter the internal environment of the icefish (temperature) and the echinoderm (ionic composition).

Regulation does not necessarily imply absolute homeostasis. In fact, few regulatory systems are "perfect," and so regulated variables invariably are not perfectly constant, i.e., there is not complete homeostasis. Nevertheless, these variables are maintained more constant by the regulatory systems than if there was no regulation. For example, the osmotic concentration of the body fluids of the shrimp *Upogebia* is regulated, but not perfectly, at a higher concentration than the medium, at least at environmental osmotic concentrations <1000 milliosmolal, by physiological mechanisms; the body fluid osmotic concentration depends on the ambient medium although it is not equal to it (Figure 2–4). Physiological mechanisms maintain the body fluids. The mechanisms for osmoregulation are discussed further in Chapter 16. Measurement of the body fluid pH of most lower animals indicates a marked effect of temperature, of about -0.014 U $°$ C^{-1},

i.e., a 10° C increase in temperature lowers the pH by about 0.14 units (which is equivalent to a 38% increase in hydrogen ion concentration). Consequently, we might suspect the lack of precise pH regulation but these animals actually are precisely regulating the ratio of H^+ to OH^- (relative alkalinity) regardless of temperature. Their pH changes parallel that of pure water at differing temperature, for which there is also about a -0.14 U $^\circ C^{-1}$. The mechanism for the regulation of H^+/OH^- is provided by the metabolic production and the respiratory excretion of CO_2 (see Chapter 15).

Thus, there are two basic patterns of how physiological variables alter with changes in the external environment: **conformation** when the internal variable is always equal to the environmental variable and **regulation** when the internal variable is kept different from the external value. If the physiological variable in question is body temperature, then the respective terms would be thermoconformation and thermoregulation. Similarly, for osmotic concentration, the terms would be osmoconformation and osmoregulation, for ionic concentration the terms would be ionoconformation and ionoregulation, etc. Animals such as *Upogebia* and *Callianassa,* which survive over a wide range of external salinities, are said to be euryhaline, in contrast to stenohaline animals, which survive over a more restrictive, narrow range of external salinities. The prefixes **eury-** and **steno-** are also applied to other physiological variables, e.g., temperature: eurythermal and stenothermal.

Other prefixes used to describe the constancy or change in an internal variable are **poikilo-** and **homeo-**. For example, an animal whose body temperature is variable is poikilothermic; the body temperature may be equal to ambient temperature, or it may alter in some other fashion as ambient temperature alters, or it may even alter while ambient temperature remains constant. The important point is that the body temperature of a poikilotherm is variable rather than constant. An animal whose body temperature remains constant is, in contrast, a homeotherm. Similar pairs of terms would be poikilo-osmotic and homeo-osmotic and poikiloionic and homeoionic. It is important to appreciate that the prefix poikilo- and the term conformation do not convey the same meaning. For example, the shrimp *Upogebia* is poikilo-osmotic at external salinities <1000 mOsm but is not osmoconforming; at higher salinities, it is both poikilo-osmotic and osmoconforming. The prefix homeo- and the term regulation are also not synonymous. For example, an icefish is a good homeotherm, but does not thermoregulate.

In summary, the prefixes poikilo- and homeo- are useful for describing whether a physiological variable is constant or variable, but they do not indicate whether there are regulatory mechanisms for that physiological variable. The terms conform and regulate are preferable when describing the absence or presence of a specific regulatory mechanism. The prefixes eury- and steno- describe whether a wide or narrow range of values is tolerated.

A final term has recently been introduced to describe a situation in which normal functioning is maintained in the absence of homeostasis. **Enantiostasis** is the maintenance of function when the effect of a change in one physiological variable is counteracted by a change in another physiological variable (Mangum and Towle 1977). For example, blue crabs transferred from seawater to brackish water experience a decrease in body fluid osmotic and ionic concentrations and an increase in the pH because of higher hemolymph ammonia levels. The lower salt concentration of the hemolymph decreases the affinity of its respiratory pigment hemocyanin for oxygen but the higher pH increases the affinity of hemocyanin and counteracts the effect of lowered salt concentration. Oxygen transport by the respiratory pigment is therefore not as compromised by transfer to brackish water as expected. Homeostasis of function, or enantiostasis, has occurred in the absence of homeostasis of two important physiological variables, salt concentration and pH. The significance of this example of enantiostasis is to emphasize the complexity of physiological functioning and the important interactions that can occur between different physiological variables. The recent introduction of this new term illustrates the limitations of terminologies in describing complex, interrelated physiological processes.

Tolerance and Resistance

Animals either conform or regulate in the face of moderate environmental change. Eventually they become unable to tolerate further extreme change and die; regulators are unable to regulate and their internal environment alters to an extent incompatible with normal cellular functioning; conformers experience sufficient changes in their internal environment that normal cellular functioning is disrupted.

The range of any specific environmental variable that an animal can survive is called its **range of tolerance**. Above and below the critical values at the extremes of the ranges of tolerance are **ranges of resistance**, in which the animal is not quickly killed but will eventually die. An example of ranges

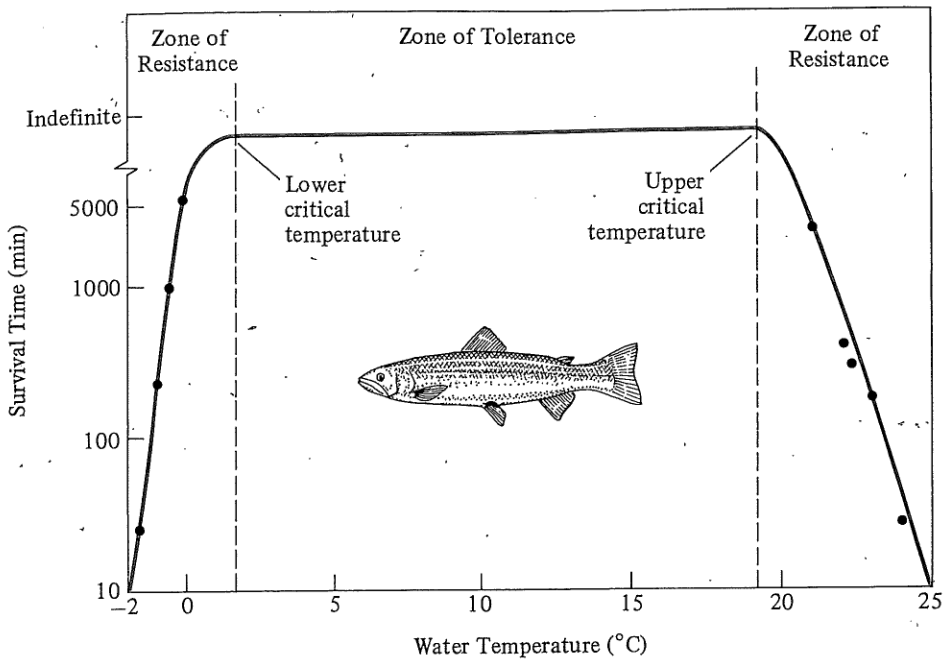


FIGURE 2–5 Ranges of tolerance and resistance to high and low temperatures for young chum salmon *(Oncorhynchus keta)* acclimated to a water temperature of 5° C. An experimentally determined survival time longer than 5000 minutes was interpreted to indicate indefinite tolerance to that temperature. The lower and upper critical temperatures are approximately 0° C and 20° C respectively, with this acclimation regimen. *(Data from Brett and Alderice 1958; Brett 1952.)*

of tolerance and resistance is illustrated by the temperature tolerance of fish (Figure 2–5). The survival time is indefinite for temperatures within the range of tolerance, but declines to zero at the extremes of the lower and upper ranges of resistance.

Experimental determination of survival, above the critical maximal value or below the critical minimal value, is fairly straightforward, although there is individual variability in tolerance. The relationship between survival time and level of exposure is usually sigmoidal (S-shaped) over a range of physiological values. The classical means for determining the average tolerance to death is to estimate the level that is lethal for 50% of the experimental subjects. This value for 50% survival (and 50% mortality) is called the LT_{50} (lethal tolerance for 50%). Similar sigmoidal relationships are observed for response as a function of drug dosage (LD_{50}), and lethal concentrations of toxin (LC_{50}), as a function of dosage. Typically, a graph of the accumulated mortality yields a sigmoidal or curvilinear relationship with the physiological variable, e.g., mortality of carp as a function of ammonia concentration (Figure 2–6A). The LD_{50} can be determined from such a graph by extrapolation of the data through the 50% line. The sigmoidal or curvilinear relationship can be converted to a straight line, to facilitate determination of the LD_{50} value, by a probit transformation (Figure 2–6B). Physiologists generally prefer straight-line relationships over curvilinear relationships because of their greater ease of statistical analysis by least-squares linear regression, which allows the determination of the intercept (± its standard error), slope (± its standard error), correlation coefficient (r), and 95% confidence limits.

Acclimatization and Acclimation

The range of tolerance for a species, or even individuals within a specific population, is not rigid and unalterable. In fact, animals are generally able to readjust their range of tolerance over a period of time in response to alterations in their external environment, i.e., animals adjust to their environment. **Acclimatization** is the term used to describe this readjustment phenomenon when it is observed

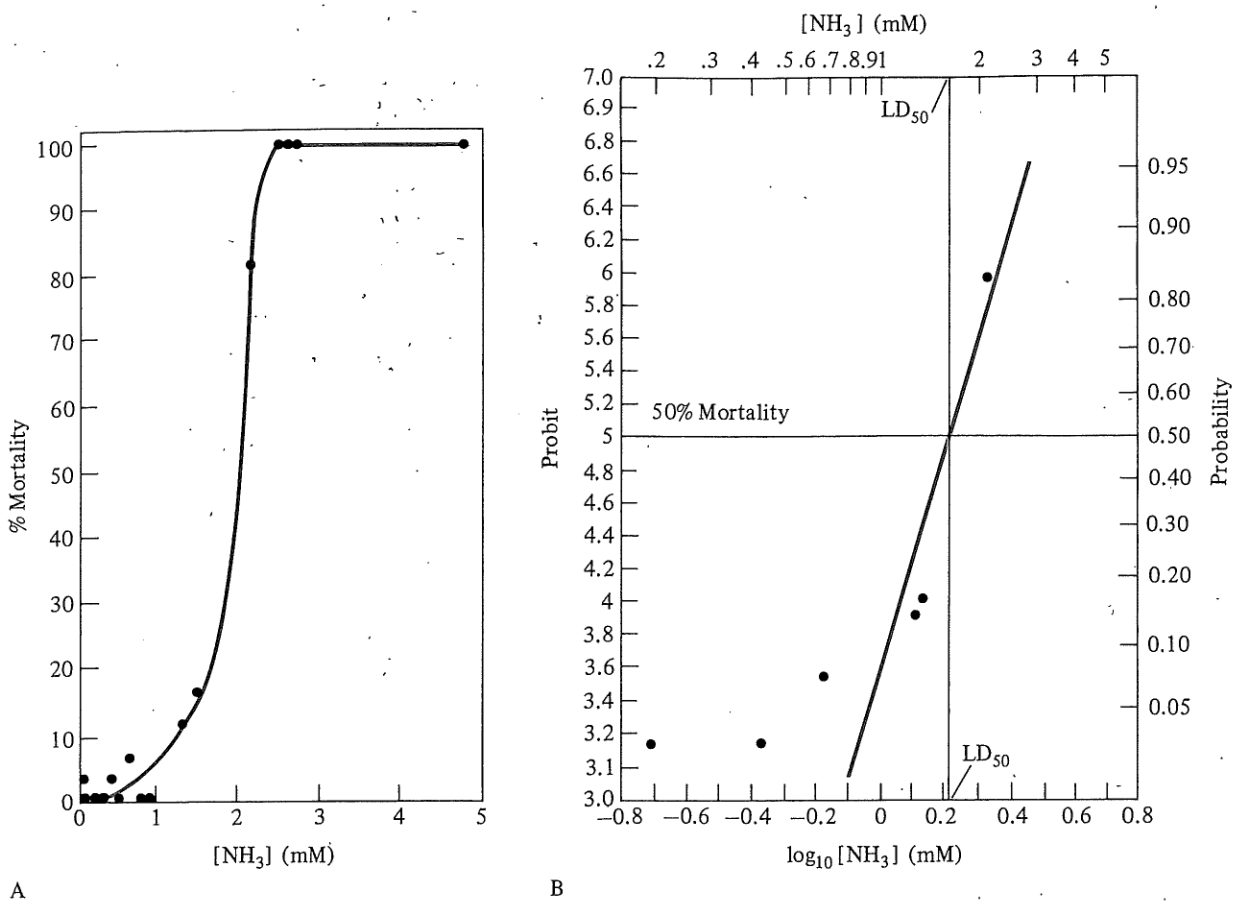


FIGURE 2–6(A) Dosage % mortality relationship for the toxic effects of ammonia on carp. Note the curvilinear relationship between % mortality and dosage on arithmetic scales. **(B)** The linear relationship using logarithmic scales and probit plot for the dosage % mortality curve for carp (data from part A). The latter relationship allows determination of the regression line (solid line). The LD_{50} is 1.68 mM NH_3. *(Data from Hasan and Macintosh 1986.)*

in the natural environment. For example, an alteration in the upper critical temperature of a species of fish in response to seasonal changes in water temperature is thermal acclimatization (see Chapter 5). The physiological adaptation of an animal's range of tolerance to an altered environment, when investigated under the controlled conditions of a research laboratory, is called **acclimation**, rather than acclimatization.

Acclimation and acclimatization generally occur in the "appropriate" direction. For example, the upper critical temperature of an aquatic fish is higher during summer when water temperatures are higher, and the lower critical temperature is lower during winter when the water temperatures are lower. Similar adaptive alterations are observed in the critical thermal maxima and minima of fish acclimated in the laboratory to varying water temperatures (Figure 2–7). It may be more appropriate for other physiological functions, such as rate functions (metabolic rate, heart rate, respiratory rate, etc.), to alter in different ways from parameters such as upper and lower critical temperatures. For example, it might be appropriate for metabolic rate to remain unaltered by a change in environmental temperature (see thermal acclimation and metabolic acclimation in Chapter 5).

Regulatory Mechanisms

We have already seen that homeostasis does not necessarily require a regulatory mechanism; the constant body temperature of an Antarctic icefish illustrated this point. Any such example of an internal variable being in equilibrium with an external environmental variable could result in **equilib-**

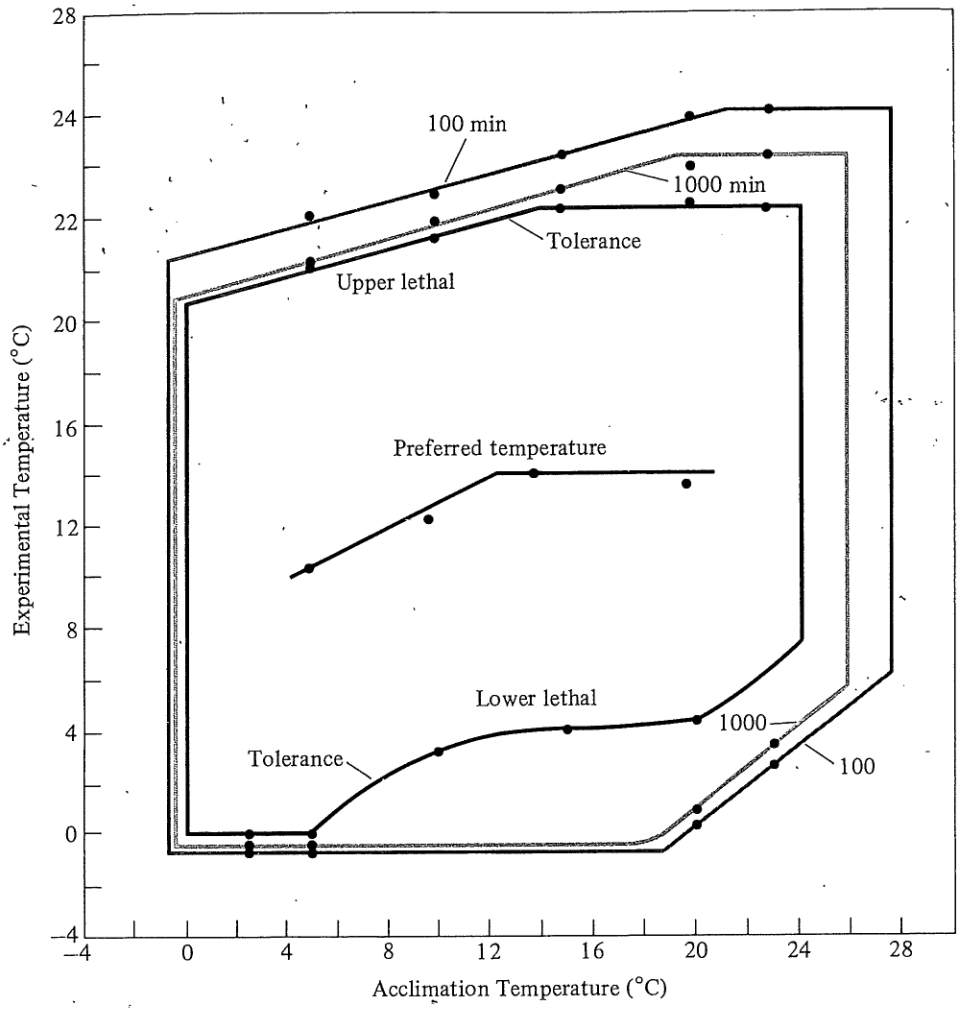
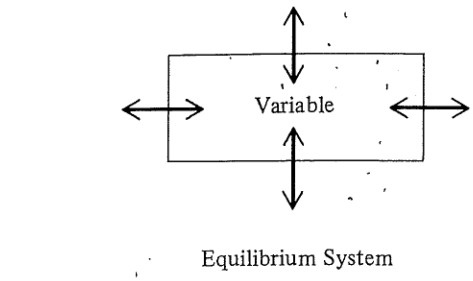


FIGURE 2–7 The thermal tolerance polygon for young chum salmon *(Oncorhynchus keta)* acclimated to water temperatures from 0 to 25° C shows the upper and lower lethal temperatures for indefinite tolerance (inner color polygon) and the temperatures for 1000 and 100 min tolerance (outer polygons). For example, a salmon acclimated to 12° C has an upper lethal temperature of 22° C and a lower lethal temperature of 4° C for indefinite exposure, but will survive 100 minutes at 22.2° C and −0.3° C. The preferred body temperature selected by the salmon in a thermal gradient is also indicated. *(Modified from Fry and Hochachka 1970; after Brett 1952; Brett and Alderdice 1958.)*

rium homeostasis, without the necessity of any regulatory mechanism (Figure 2–8A). However, few physiological variables in only some animals are ever in equilibrium with the external environment.

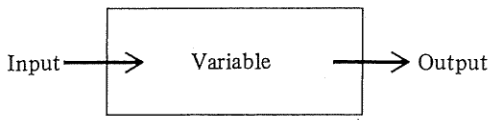
Homeostasis can occur in the absence of a regulatory mechanism even if the animal is not in equilibrium with the external environment as long as a steady-state condition is maintained. Consider a molecule "X" that is liberated into the body fluids at a constant rate (e.g., X might be a metabolic end product). X is eliminated from the body fluids at a rate proportional to its concentration in the body fluids; the concentration of X will increase until the rate of elimination equals the rate of release. Then, the concentration of X will remain constant at a steady-state value. The actual concentration of X depends on the rate of release and the concentration dependence of its rate of elimination. This **steady-state homeostasis** is an open system, since there is no apparent regulatory mechanism linking the concentration of X to either its production or elimination (Figure 2–8B).

An example of a steady-state open system is the average blood concentration of an important reproductive hormone, luteinizing hormone (LH), in female mammals. LH is released into the blood



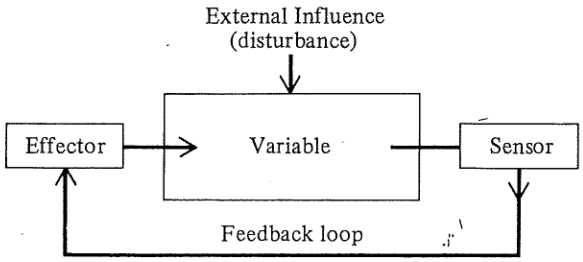
Equilibrium System

A



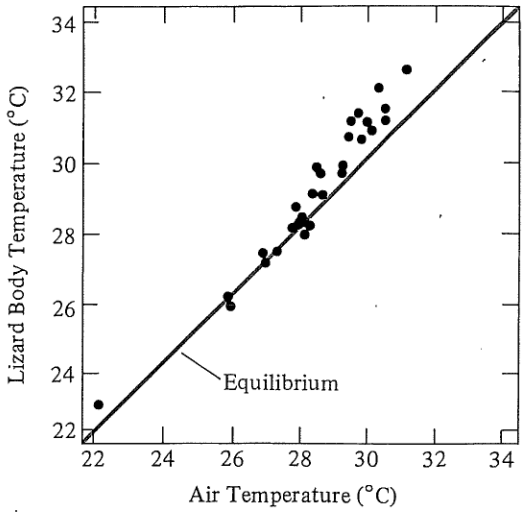
Open System

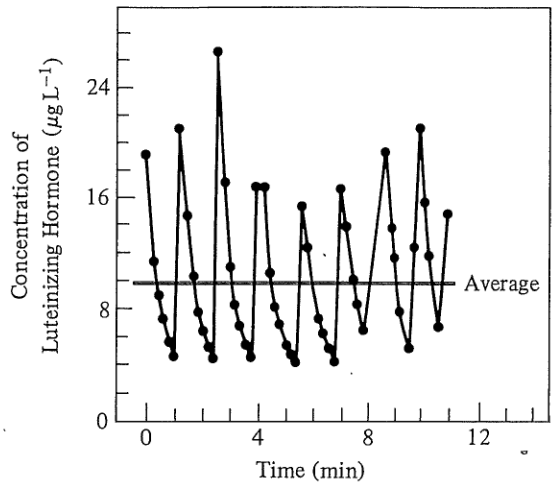
B



Closed Feedback System

C





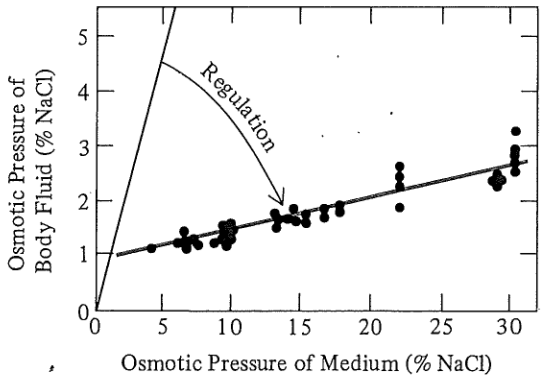


FIGURE 2–8 Three models resulting in relative homeostasis. **(A)** For a static equilibrium system in a constant environment, the value of an internal variable is constant if it is in equilibrium with an external value that is constant. For example, the body temperature of a forest-dwelling lizard is essentially the same (dots) as the air temperature (line). **(B)** In an open loop dynamic equilibrium system, the value of an internal variable is determined by the rate of input and the rate of elimination, which is concentration dependent. For example, the average blood LH concentration in ewes is determined by the rate of pulsatile release. **(C)** A feedback control loop results in a dynamic equilibrium between the effect of an external disturbance with the value of the variable determined by an internal setpoint and monitored by a sensor system that provides information to an effector system. The level of the regulated variable is kept relatively constant despite dramatic changes in the disturbance. For example, the body fluid composition of brine shrimp is maintained relatively constant (dots) in external media of widely differing concentration (black line).

from the anterior pituitary gland in pulses; it is then eliminated from the blood by a variety of mechanisms (tissue uptake, metabolism, urinary excretion). The concentration of LH in the blood increases during periods of release, then declines in the intervening periods of nonsecretion owing to its clearance from the blood, but the average concentration of LH in the blood is quite consistent over time, with the mean value depending on the frequency of episodic release. For example, ewes with a higher frequency of LH release have a higher mean concentration of LH than ewes with a low frequency of release (Karsch 1980). There are also regulatory mechanisms for the control of blood LH levels (see Chapter 11, Endocrinology).

Another mechanism for homeostasis involves a specific physiological mechanism for the regulation. A particular physiological variable is regulated at, or near, a specified value of the variable, i.e., a setpoint. The actual value of the physiological variable is monitored by a sensory system. Information from the sensory system is used to control the value of the variable through some effector system. There is a feedback loop from the value of the variable, via sensory and effector mechanisms, that controls the value of the variable at the setpoint despite external disturbances to the variable. The four essential elements of such a regulatory system—setpoint, sensor, feedback, and effector—are unique to this form of regulated, feedback homeostasis. This **regulatory feedback homeostasis** is a closed system, in contrast to the open equilibrium and steady-state systems. An example of feedback regulation is the control of hemolymph osmotic concentration by the brine shrimp *Artemia* (Figure 2–8C). The regulated variable is hemolymph osmotic concentration and the effector mechanism is branchial salt pumps.

Let us now examine the basic principles involved in feedback regulation of a closed system by example. A hot water bath maintained at a prescribed temperature by a heating element is a simple, and familiar, engineering regulatory system (Figure 2–9A). The components corresponding to the four elements of a feedback regulatory system are a setpoint (the position of a switch on a thermometer scale), the sensor (a bimetallic spiral strip thermometer), feedback (the open or closed position of the switch), and the effector (a current source and heater element). The setting of the thermostat control of

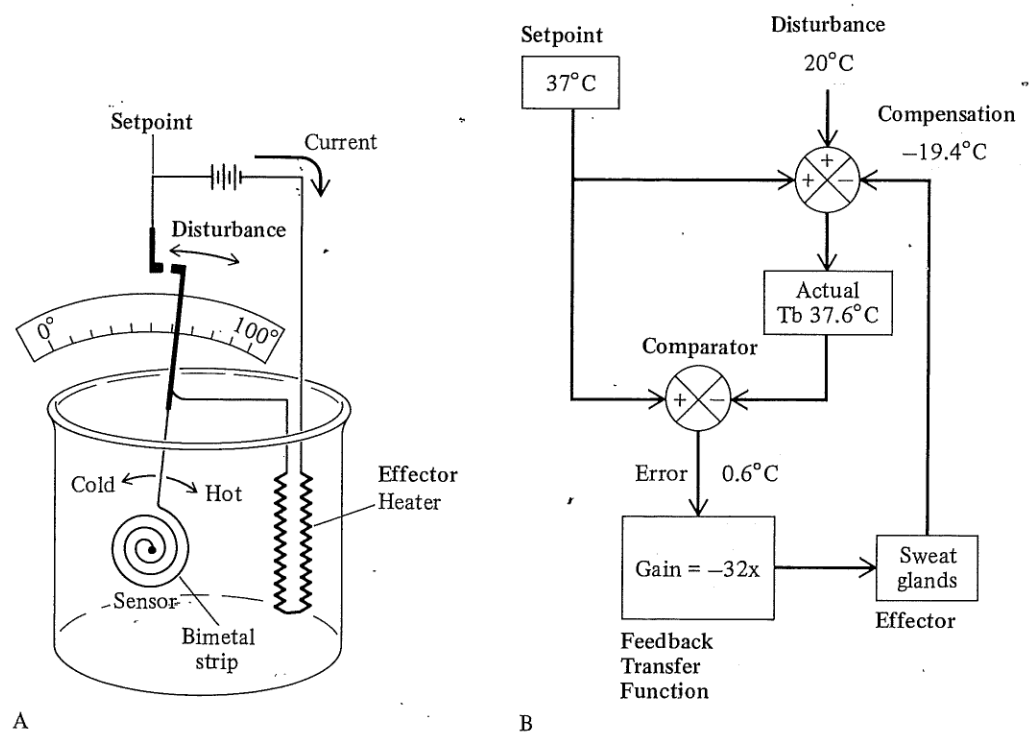


FIGURE 2–9(A) The principles of negative feedback regulatory systems are well illustrated by a simple engineering example of feedback regulation of water temperature by a water bath heater. **(B)** Schematic outline of the elements of a negative feedback regulatory system.

the bath water determines the theoretical value at which the water will be maintained, e.g., $T_{setpoint}$ = 50° C. The sensor switch keeps power supplied to the heater element as long as the temperature of the water is less than the $T_{setpoint}$ of 50° C, because the tension of the bimetallic strip keeps the switch contacts closed. Heating stops when the temperature recorded by the thermometer exceeds the setpoint and the switch contacts open. This is a relatively simple "On–Off" regulatory system, capable of only moderate precision of water temperature regulation (e.g., ± 2° C might be typical for such a water bath).

Some physiological control systems operate as "On–Off" regulators, but systems with proportional control are capable of far greater precision of regulation (Figure 2–9B). Proportional control means that the magnitude of the effector response (e.g., rate of heating) is proportional to the error (deviation of the actual temperature from the setpoint), thus providing rapid heating when the water temperature is much lower than the setpoint (e.g., 20° C) but lower heating when the temperature is closer to the $T_{setpoint}$ (e.g., 45° C).

The setpoint value of a proportional physiological regulatory system is exactly analogous to that of the "On–Off" bath water example, i.e., it is the value at which the regulatory system is attempting to maintain the physiological variable. For example, the setpoint for the human temperature regulatory system is about 37° C; for the arterial blood pressure system it is about 13.2 kPa (100 torr). The actual value of the physiological variable (temperature, blood pressure, etc.) is determined by a combination of the setpoint value, the extent of disturbances on the system, and the degree of compensation by the regulatory system. The convention in a model of a control system is to assign the setpoint value a positive sign, the disturbance a positive sign indicating that it would increase the variable value, and the compensation a negative sign, since it will counteract the disturbance. A substantial increase in air temperature or a radiative heat load, for example, might be sufficient to elevate a human's body temperature by 20° C in the absence of a thermoregulatory system; the disturbance is +20. In this particular example of body temperature regulation, the compensation might be −19.4° C (see below). The actual value of the body temperature is then

$$\begin{aligned}\text{actual body temperature} &= \text{setpoint} \\ &\quad + \text{disturbance} \\ &\quad - \text{compensation} \\ &= 37 + 20 - 19.4 \\ &= 37.6^\circ\text{C} \end{aligned} \qquad (2.2)$$

The actual body temperature is compared with the setpoint by a comparator in order to determine the difference (error) between the two terms, e.g., error = 37.6 − 37 = 0.6° C. The error is then processed according to some specific relationship between error and degree of compensation. This relationship, called a **transfer function**, is specific for the particular regulatory system involved. It can entail amplification (or multiplication by a constant factor); addition, subtraction, or multiplication by numerous inputs; multiple algebraic operators; integration; etc. The net effect of the transfer function is to convert the error signal into a compensation signal. In the human thermoregulatory system, for example, the transfer function is multiplication by the constant value of 32, i.e., compensation is 32 × error.

The gain of the regulatory control system is defined as the compensation relative to the remaining error.

$$\text{gain} = \text{compensation/remaining error} \qquad (2.3)$$

Gain reflects the conversion of the error into a compensation; a gain >1 indicates amplification and <1 reflects attenuation. The negative sign indicates that the gain is inverting, so that the compensation is in the opposite direction to the error. For the thermoregulatory system, gain = −19.4/0.6 = −32. This is a fairly high gain for a control system, indicating that body temperature is quite precisely regulated. The gain of the baroreceptor system for regulation of arterial blood pressure is substantially lower, at about −7, reflecting relatively poor regulation. However, other regulatory mechanisms also operate in concert with the baroreceptors for precise, long-term regulation of mean arterial blood pressure. The gains for other physiological regulatory systems vary dramatically from close to 0, to −20, to −50, or even to −infinity.

A general consequence of feedback regulation is that the actual value of the physiological variable is different from the setpoint value, except when there is no disturbance. The magnitude of the difference between the actual and setpoint values at steady-state depends primarily on the gain. The greater the gain, the lower the deviation of actual value from setpoint value.

A few regulatory control systems are perfect. The actual value of a variable is regulated equal to the setpoint value, i.e., there is negative infinite gain. One example of a perfect regulatory system is the regulation of arterial blood pressure by the human kidney (Figure 2–10). The amount of water excreted by the kidneys is a function of the mean arterial blood pressure; an elevation in pressure

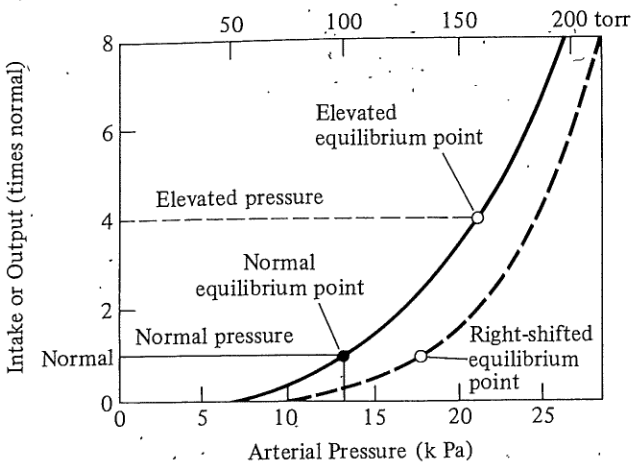


FIGURE 2–10 There is infinite-gain regulation of mean arterial blood pressure in humans by the renal control of fluid loss. The normal equilibrium point is eventually regained after any disturbance that either increases arterial blood pressure (and results in elevated fluid excretion) or decreases blood pressure (resulting in a renal fluid loss less than fluid intake). The mean arterial blood pressure can be elevated by either a chronic increase in fluid intake and loss (thin dashed line) or a right shift in the curve caused by elevated blood angiotensin levels (thick dashed curve).

elicits a greater renal fluid loss. Part of the excreted fluid comes from the circulatory system, and any decrease in circulatory fluid volume causes blood pressure to decline. Thus, if arterial pressure is increased by a disturbance, then the rate of renal water excretion is elevated, the circulatory fluid volume is reduced, and blood pressure declines to the setpoint value. The opposite scenario serves to elevate blood pressure if some disturbance causes arterial pressure to drop. This is the normal renal regulatory mechanism for long-term blood pressure regulation. Chronic elevation of blood pressure can be caused by two mechanisms: increased fluid and salt intake, and alteration of the position of the relationship between renal fluid excretion rate and mean arterial pressure. An increase in water intake necessitates an increased renal loss, which is accomplished by/causes an elevation of mean arterial blood pressure. Alternatively, a shift in the position of the relationship—a right-shift caused, for example, by elevated levels of a hormone (angiotensin)—will result in an elevated mean arterial pressure at the normal rate of fluid intake and loss.

Negative and Positive Feedback. The direction of compensation must be opposite to the direction of the disturbance for a feedback system to regulate the value of a physiological variable; the feedback must be negative. For example, the compensation must decrease body temperature if the disturbance elevates body temperature, and vice versa. There are innumerable examples of **negative feedback regulation** in physiological systems: blood glucose regulation by insulin, regulation of mean arterial pressure by baroreceptors and renal fluid loss, plasma calcium level regulated by the hormone parathormone (and also calcitonin), body temperature regulation in mammals and birds, and chemical regulation of respiration.

Positive feedback regulation occurs when the compensation augments the disturbance. Positive feedback clearly has detrimental consequences for homeostasis; it destabilizes the regulated variable. For example, a considerable blood loss decreases the blood volume to such an extent that there is insufficient blood flow to the heart muscle. This inadequate blood flow causes anoxia of the heart muscle, and so the heart fails to pump at a normal rate and pressure, lowering cardiac output. This in turn decreases blood pressure, causing a further drop in blood supply to the heart. Thus, a positive feedback, or vicious cycle, is initiated and can rapidly lead to circulatory collapse and death.

Positive feedback cycles are often used for beneficial, though nonhomeostatic, functions by animals. Positive feedback can initiate an extremely rapid change. For example, the rapid generation of an action potential by a nerve or muscle cell is due to positive feedback between membrane electrical potential and the permeability of the membrane to sodium ions. The membrane electrical potential rapidly increases during an action potential from about -100 mV to about $+40$ mV. The details of the neurophysiological processes involved are presented in Chapter 6, but a general discussion of the concept of positive feedback mechanisms is of interest here. If some external stimulus depolarizes the resting membrane potential (e.g., changes it from -100 to -90 mV), then this increases the sodium ion permeability by opening sodium channels through the membrane (Figure 2–11). The increased sodium permeability causes an influx of Na^+ into the cell, further depolarizing the membrane and, in a regenerative fashion, increasing the sodium permeability even more. A positive feedback cycle is thus initiated, and it causes a rapid increase in membrane potential. The timing of the cycle is also important; the early phases of change in sodium permeability are more rapid than the final phases. The positive feedback cycle ends only when all of the sodium channels are open and sodium permeability is maximal. How does the sodium permeability

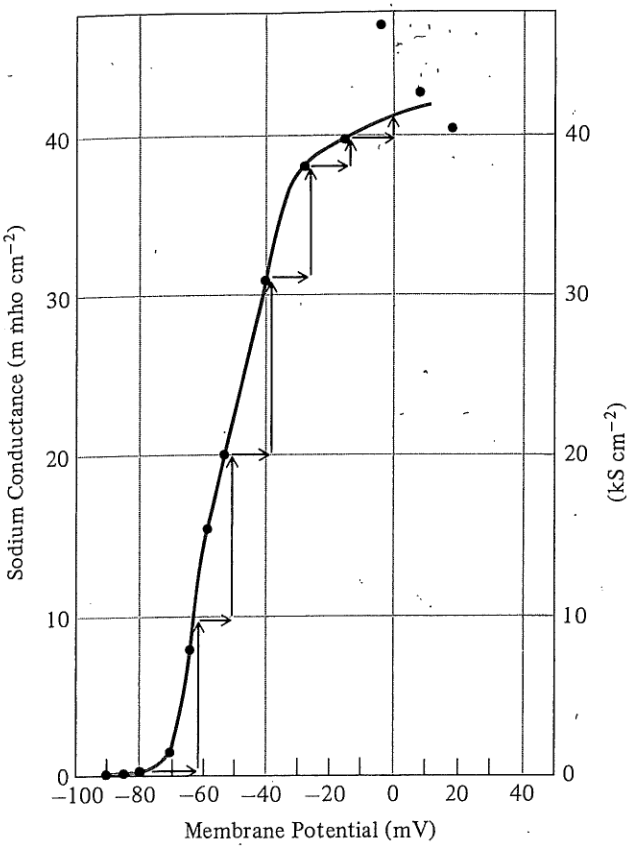


FIGURE 2–11 There is a positive feedback relationship between the resting membrane potential of nerve cells (E_m) and the sodium conductance (g_{Na}^+). A depolarization of E_m towards 0 mV results in an increased g_{Na}^+, which in turn causes a further depolarization of E_m. The positive feedback effect is shown as a series of step changes in E_m and g_{Na}^+ (light arrows), but in reality the positive feedback results in a smooth depolarization of E_m and increased g_{Na}^+ (solid line). Units for Na^+ conductance are $k\Omega^{-1}$ (or mmho) cm^{-2} and kSiemens cm^{-2} (1 S = 1 mho). *(Data from Hodgkin and Huxley 1952.)*

ever return to normal? Positive feedback would prevent any decrease in sodium permeability, so some other factor is involved. The sodium channels have an inherent property of automatically closing after they have opened, regardless of the membrane potential, and this ensures a return to initial resting conditions.

A second example of positive feedback involves one aspect of the endocrine regulation of reproduction in female mammals. Estrogen secreted from the ovaries causes a rapid surge in secretion of LH (luteinizing hormone) from the anterior pituitary immediately prior to ovulation. The elements for positive feedback are high estrogen levels promote LH secretion by the anterior pituitary, then elevated LH levels promote estrogen secretion by the ovaries. Other examples of positive feedback include the emptying of body cavities—swallowing, defecation, birth—and blood clotting. These are all nonhomeostatic functions.

Multiple Control Systems. The level of important physiological variables is often controlled by not one, but multiple, regulatory effectors. Multiple control systems increase the precision of regulation and provide greater flexibility of regulation through the higher complexity of the sensory, feedback, and effector systems.

The behavioral thermoregulatory system of many lizards provides a clear example of a dual regulatory system, even at the level of simply observing the behavior of the lizards. Most lizards thermoregulate by basking in direct sunlight or on warm substrates (see Chapter 5). Lizards will move into a favorable basking location when their body temperature is below some lower setpoint in order to warm up to their "preferred" body temperature. However, the lizard will move to a cooler location if its body temperature rises above an upper setpoint. Lizards can be readily observed in the field and laboratory to "shuttle" with some regularity between cool and warm locations in order to keep their body temperatures within the narrow "preferred" body temperature range. The thermoregulatory mechanisms of such lizards have been hypothesized to have a dual thermostat (Figure 2–12). A low setpoint thermostat determines movement to a warm environment if body temperature < low setpoint; the movement causes a heat gain that elevates body temperature into the preferred range. A high setpoint thermostat initiates movements to a cooler environment, if body temperature > high setpoint, and lowers body temperature into the preferred range. There is also input of peripheral temperature receptors into the thermoregulatory control system via the reticular formation in the brain, which modifies the operation of the dual setpoint hypothalamic system. The dual thermostat system provides a fairly precise regulation of body temperature regulation. The precision of thermoregulation depends upon how close the upper and lower setpoints are.

A second example of a dual thermostat thermoregulatory system, but of entirely different mechanisms, is observed in mammals. Mammals can regulate their body temperatures through physiological, in addition to behavioral, means. Internal heat production is increased by elevated cellular metabolism to elevate body temperature if it drops

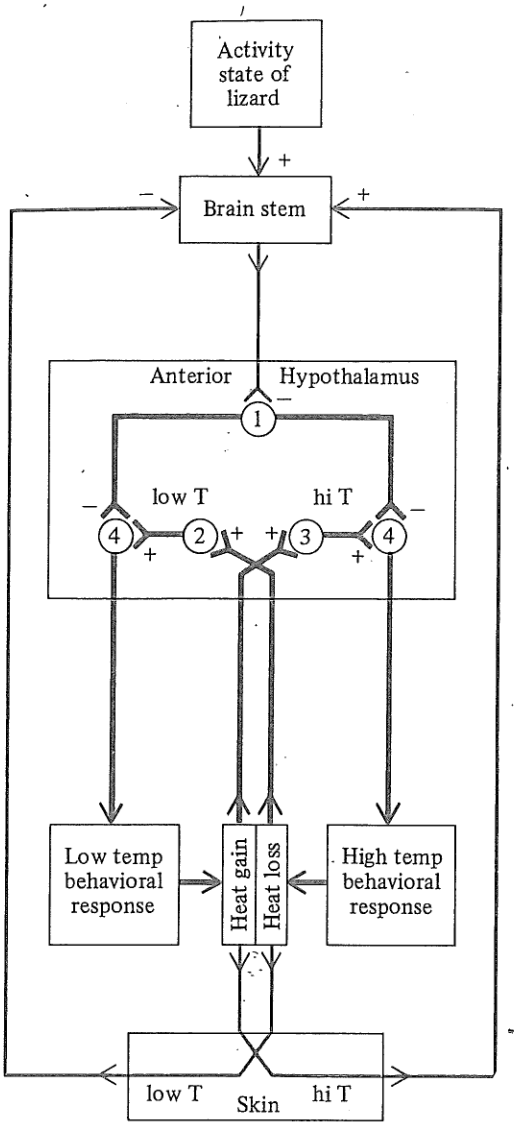


FIGURE 2–12 Hypothetical neural network illustrating the dual setpoint model of body temperature regulation by lizards. The anterior hypothalamus contains temperature-insensitive neurons (1), cold-sensitive neurons (2), warm-sensitive neurons (3), and motor neurons (4) responsible for low and high temperature shuttling activity. Shuttling into a warm environment causes heat gain, which elevates the anterior hypothalamic temperature and stimulates the high temperature receptors, eventually eliciting heat-avoidance behavior (heavy lines). The peripheral temperature-sensitive neurons of the skin feed information back to the reticular formation of the brain stem (light lines), thence to the anterior hypothalamus, that reduces the firing activity of the temperature-insensitive neurons. Shuttling into a warm environment elicits the opposite responses. The general activity state of the lizard could also influence the activity of the reticular formation; a high activity level would increase the activity of the reticular formation. *(Modified from Berk and Heath 1975.)*

below a lower setpoint. Heat is dissipated through evaporative (and other) means if body temperature exceeds an upper setpoint. Both of the thermostats are located in the hypothalamus, deep within the brain, and consequently the regulated variable is hypothalamic temperature rather than body temperature measured elsewhere (e.g., oral, esophogeal, rectal). The low setpoint for metabolic heat production is approximately 36.8° C (if skin temperature is 30° C; see below); heat production is increased at body temperatures below this setpoint, and remains stable at body temperatures above the setpoint (Figure 2–13). The high setpoint that initiates evaporative heat loss, by sweating, is about 37.3° C (if skin temperature is 30° C); body temperatures above this setpoint result in progressively higher rates of evaporative heat loss. These hypothalamic thermoreceptors are clearly not the only temperature sensors in the body; for example, the integument is well endowed with both cold and hot thermoreceptors. These peripheral thermoreceptors also contribute to the operation of the thermoregulatory control system by altering the lower and upper setpoints for metabolic heat production and evaporative heat loss, and also by altering the gains for the two transfer functions (the slopes of MHP and EHL versus hypothalamic temperature in Figure 2–13).

Oscillation and Damping. We have seen an example of how a physiological variable, the blood concentration of luteinizing hormone (LH), can **oscillate** owing to episodic pulsing of LH release with subsequent clearance (Figure 2–8B); this oscillation occurs in an open system. Similar oscillation, or "hunting," can occur in negative feedback, closed systems if some of the elements have inertia (slowness of response), or if there are delays in the feedback loop. Let us return to our example of a hot water bath. If the water bath had a small, unstirred volume of water and a massive heating element with a high rate of heat output, then it is easy to imagine that the rapid rate of heating of the element would quickly add so much heat to the water that, because of the large amount of heat remaining in the heater element, the temperature would not only rise rapidly to the setpoint of 50° C, but would overshoot the setpoint even after the thermostat opened the contacts and turned off the heater. The temperature would then slowly decline by passive heat loss to the environment until it fell below the setpoint of 50° C. The heater element would then be turned on, rapidly overheat the water, and the extreme temperature cycle would repeat itself. This tendency to oscillate, and the magnitude

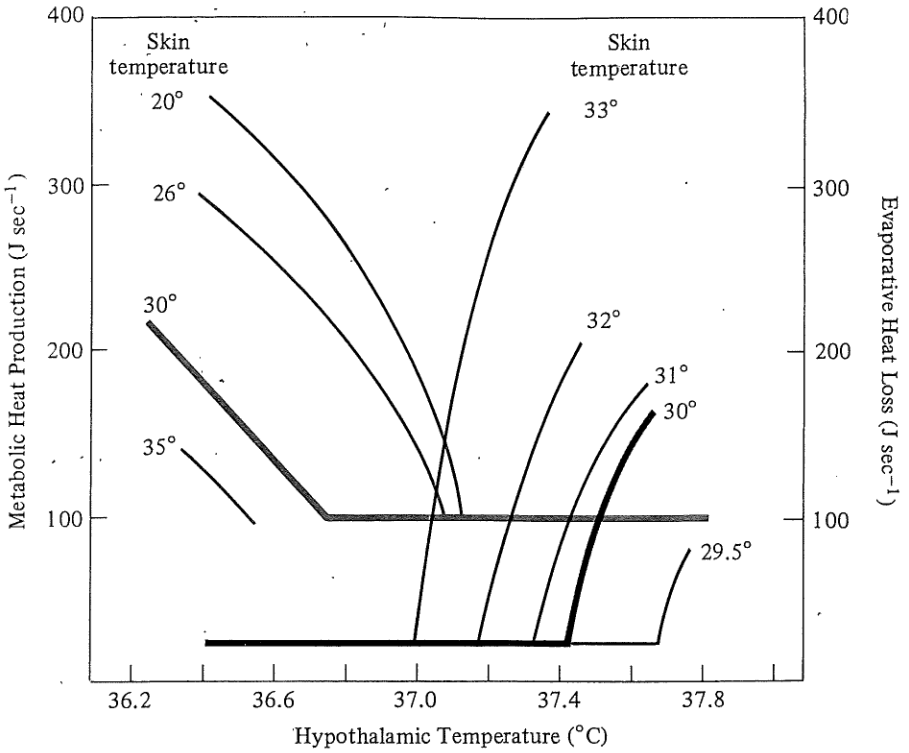
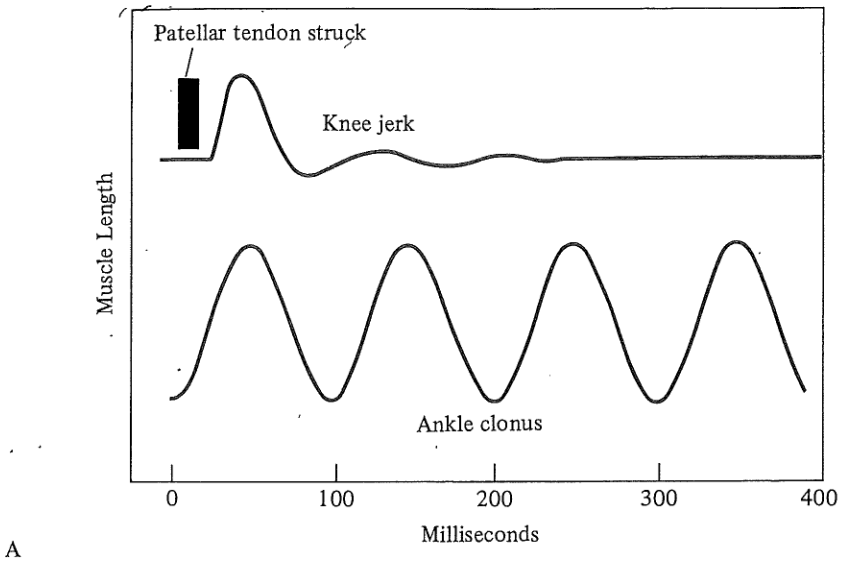


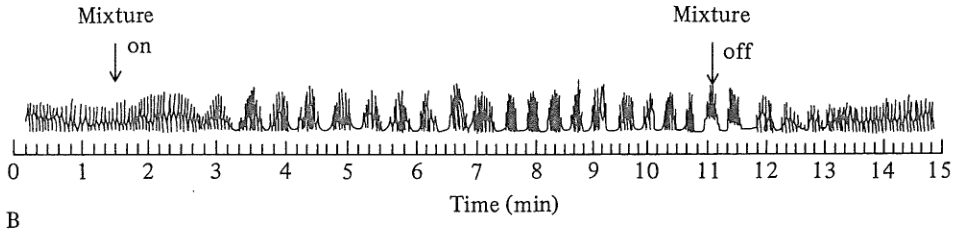
FIGURE 2–13 Body temperature regulation in humans involves elevation of metabolic heat production during cold stress (decreased anterior hypothalamic temperature) and evaporative heat loss during heat stress (elevated anterior hypothalamic temperature). The low setpoint (T_{low}) is about 36.8° C for control of metabolic heat production, and the high setpoint (T_{high}) is about 37.3° C for control of evaporative heat loss (heavy lines are relationships for a skin temperature of 30° C). Peripheral skin temperature receptors also influence the low and high setpoints and the slopes of the relationships of metabolic heat production and evaporative heat loss to hypothalamic temperature (light lines). *(Modified from Benzinger 1964.)*

of the oscillation, would be diminished by decreasing the inertia of the regulatory effector system, i.e., reducing the thermal capacity of the heater element or increasing the water volume. A delay between turning the heater ON and OFF and closing the temperature sensor contacts (e.g., poor water mixing) could also cause oscillation. Elimination of such time delays, for example, by keeping the water well-stirred, would minimize the tendency for oscillation. Finally, oscillation can be exacerbated by an extremely high gain.

Oscillation in physiological control systems is well illustrated by the knee jerk reflex and other stretch reflexes. When the knee jerk reflex is initiated by striking the patellar tendon, the quadriceps muscle is stretched. It then contracts in response to its stretching, and this causes the lower leg to jerk forward. The myogram (recording of muscle length) of this dynamic stretch reflex (Figure 2–14A) shows a rapidly disappearing oscillatory cycle of quadriceps contraction and relaxation. The tendency to oscillate becomes more pronounced if the dynamic stretch reflex is facilitated by stimulation from the brain. Sensitization of the reflex can result in such a high gain that a prolonged oscillation of the ankle, called clonus, may occur. Normally, the tendency for oscillation is minimized by damping and clonus doesn't occur. However, clonus can occur under pathological conditions and can be demonstrated experimentally in decerebrate animals (animals in which the higher centers of the brain are severed from the brainstem). Oscillation can also be demonstrated in other physiological systems under experimental, or abnormal, conditions. The respiratory rhythm is generated by the respiratory center in the brain stem and normally is extremely regular. The basic respiratory rhythm is modified by a chemoreceptor (chemical sensor) regulatory



A



B

FIGURE 2–14(A) Recordings of muscle length (myograms) showing the normal minor oscillation in quadriceps length after the patellar tendon is struck (upper) and the continual oscillation of gastrocnemius length during ankle clonus. *(From Guyton 1986.)* **(B)** Normal respiratory rhythm of J. S. Haldane and periodic, oscillatory respiratory pattern when breathing an air mixture of 11.05% O_2 and 0.7% CO_2. *(From Haldane 1935. Respiration. Clarendon Press, Oxford. Copyright Oxford University Press; reproduced by permission of the Oxford University Press.)*

mechanism, which monitors the pO_2 and pCO_2 of arterial blood, and the pH of brain tissue near the respiratory center (see Chapter 13). Breathing air of a low pO_2 (but not a correspondingly high pCO_2) can cause a prolonged instability of the respiratory rhythm. The recording of the respiratory rhythm shows such a pronounced oscillation when breathing air containing 11.05% O_2 and 0.7% CO_2 (Figure 2–14B). Respiratory oscillations like this are called Cheyne-Stokes breathing, and consist of episodes of rapid breathing, punctuated by pauses. They can occur when breathing normal air at high altitudes, especially at night during sleep (low pO_2, low pCO_2); with cardiac insufficiency, since this increases the amount of time required to transport blood from the lungs to the brain (i.e., increased delay); or after brain damage that increases the gain of the respiratory regulatory mechanism.

The tendency of a negative feedback system to oscillate can be reduced by **damping** the correction signal in proportion to the magnitude of the correction signal. Damping may sometimes be accomplished by hydraulic or viscous, mechanical means. Consider a linear spring as a mechanical model for damping. The relationship between a force F_k applied to one end, and the overall extension of the spring D, is given by Hooke's law as

$$F_k = k\,(D_2 - D_1) = k\,\Delta D \qquad (2.4)$$

where D_1 and D_2 are the displacements of each end of the spring, ΔD is the net stretching of the spring, and k is the spring constant (units of force per length of spring). Application of a force will rapidly stretch the spring to its equilibrium net displacement, ΔD, i.e., $\delta D/\delta t$ is high. The rate of stretching can be reduced by incorporating a dashpot (an oil-filled

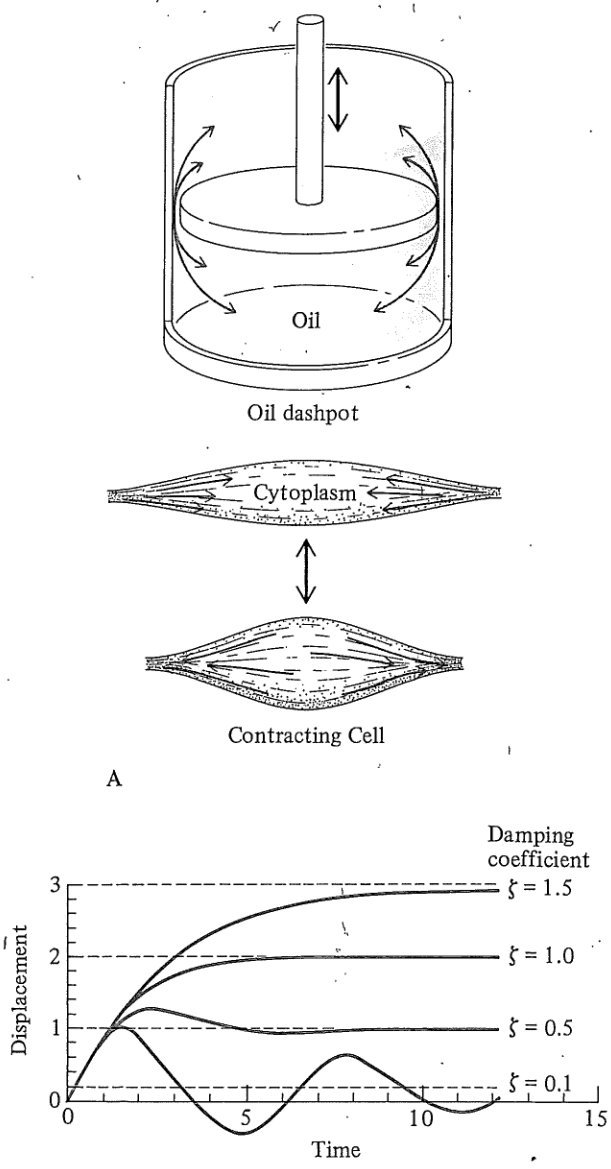


FIGURE 2–15(A) Viscous damping in a mechanical dashpot due to viscous flow of oil past the piston, and in a muscle cell due to cytoplasmic flow. **(B)** Effects of the damping coefficient (ζ) on the error of a negative feedback mechanism. A ζ of 1.0 results in rapid attainment of the new equilibrium error value after a disturbance; higher damping ($\zeta = 1.5$) causes slow movement to the new equilibrium; less damping results in slight oscillation prior to equilibrium ($\zeta = 0.5$) or pronounced oscillation ($\zeta = 0.1$). The damping coefficient is a function of inertia, time delays, and gain of the regulatory system. *(Modified from Bayliss 1966.)*

cylinder with a piston) across the ends of the spring (Figure 2–15A). Now, to stretch the spring, there must be a corresponding movement of the piston through the oil, but the high viscosity of the oil slows down the movement of the piston and therefore the rate of stretching of the spring, i.e., $\delta D/\delta t$ is reduced. Damping doesn't prevent the eventual stretching of the spring by displacement ΔD. The rate of stretching is damped by the dashpot exerting a force F_{damp}

$$F_{damp} = -B(\delta D/\delta t) \qquad (2.5)$$

where $-B$ is the damping constant, and the negative sign indicates that the damping force resists the stretching force. A dashpot is a simple mechanical example of a damping system. It is analogous however to the damping of muscle cell contraction by the necessary viscous movement of the muscle cell contents (Figure 2-15A). The damping coefficient (ζ) is a measure of the degree of damping in control systems. It is determined in a complex fashion by inertia, time delays, and gain (Bayliss 1966). A damping coefficient of 1 results in rapid adjustment after a disturbance to the new equilibrium error; coefficients >1 cause slow adjustment to the new equilibrium; coefficients <1 cause rapid adjustment with oscillation (Figure 2–15B).

Damping of biological control systems is generally accomplished by neural rather than mechanical means. The damping effect of the muscle spindle apparatus during muscle contraction is a good example. The muscle spindle is essentially a highly modified muscle cell with sensory input to the central nervous system; it monitors the degree of stretch of the muscle (Chapter 9). The muscle spindle also has motor innervation from the central nervous system (the gamma efferent fibers) that cause the muscle spindle fiber to shorten (thus mimicking stretch of the spindle by contraction of the muscle). A complex feedback of information between a muscle and the CNS via the muscle spindle normally results in smooth muscle contractions rather than jerky motions. However, the muscle contraction is jerky if the muscle spindles are destroyed.

Summary

The general physical properties of aerial, aquatic, and terrestrial environments are described, since these either influence the environment that animal cells experience or require regulatory systems to maintain relative constancy of the internal environment.

The extracellular fluids, which provide the internal environment that animal cells experience, create an internal environment that is different from the external environment. Many aspects of the internal environment are quite constant, in contrast to the external environment, i.e., there is homeostasis of the internal environment.

The mechanisms that are responsible for the maintenance of the integrity of the internal environment can include passive or dynamic equilibrium with the external environment in open systems, but generally involve feedback regulation in closed control systems. Feedback systems react to a disturbance in the value of a regulated variable. They have a fixed setpoint value, near which the variable is regulated; a comparator determines the error between the setpoint and the actual value of the variable, and the error is converted into a compensation according to some transfer function. Generally, the compensation is antagonistic to the disturbance, i.e., the system has a negative feedback system.

In some control systems the compensation augments the disturbance and destabilizes the variable, i.e., the system has a positive feedback and is nonhomeostatic. Positive feedback may be useful in producing a rapid or sustained change in a physiological parameter (e.g., action potential, emptying of a body cavity, blood clotting) or may be detrimental and compromise the regulation of a physiological parameter (e.g., circulatory collapse).

Many control systems have multiple, rather than single, negative feedback loops; thermoregulation by reptiles and mammals is an example of a multiple control system.

The particular properties of a negative feedback system can damp changes in a variable or can induce oscillation.

Recommended Reading

Bayliss, L. E. 1966. *Living control systems*. London: English Universities Press.

Cannon, W. B. 1929. Organization for physiological homeostasis. *Physiol. Rev.* 9:399–431.

Mangum, C. P. and D. W. Towle. 1977. Physiological adaptation to unstable environments. *Am. Sci.* 65: 67–75.