ONE OF THE SADDER CONSEQUENCES of the neglect of physiology as an intellectual discipline in recent years is not just what has been lost, but its reinvention as if it had never existed. Silverthorn (22) has tellingly characterized this process in terms of the knowledge of the physical principles once assumed as part of a physiologist’s conceptual toolkit. Here I would like to draw attention to how this process has affected something, if anything, even more central to what physiology is all about: the understanding of homeostasis itself.

In one sense, homeostasis is alive and well. Indeed, in trying to find newer and more exciting words for old disciplines, “homeostasis” has become a kind of respectable euphemism for the P-word. At the University of Cambridge, what used to be the first year preclinical Physiology course is now “Homeostasis” (Anatomy is “Functional Architecture of the Body” and Biochemistry is “Molecules in Medical Science”). In itself, there is perhaps no great harm in explicitly reminding students what part, at least, of physiology is about. But nearly always, what is now being taught as homeostasis is a simplistic travesty. By focusing exclusively on the most elementary kind of direct negative feedback, other types of biological control system are not mentioned; more seriously (if only because it has such direct implications for understanding the disorders of physiological regulation) the idea of a hierarchy of homeostatic control systems is left out as well.

That homeostasis must be subtle and flexible was well understood by previous generations of physiologists. As Walter Cannon wrote in Wisdom of the Body (1932): “The word does not imply something set and immobile, a stagnation. It means a condition—a condition which may vary, but which is relatively constant.” One is struck in Cannon’s writing by his intuitive understanding of nearly all the varieties of homeostatic mechanism known to control engineers: internal feedback, feed-forward, prediction, parametric feedback, hierarchical control. He also discusses the existence of reserves, and their regulation through “overflow,” and the problems posed by eating and drinking—activities that are ultimately homeostatic, but cause temporary disturbance. During the following decade, the development of the complex yet robust control systems needed to fly a bomber or point the guns on a battleship brought control theory rapidly to a kind of maturity, and helped convince many biologists that the equally complex control of the body ought to be amenable to the same kind of analysis.

The concepts of control theory began to be brought to bear on physiological problems, and by the late 1960s there were many first-rate textbooks of biological control theory that could be read and applied by students of physiology (15, 16, 20, 23). But now a generation of molecularly oriented biologists has grown up unfamiliar with the ideas of these pioneers, or with even the rudiments of control theory. Among today’s physiologists there is generally more pious lip service paid to homeostasis than genuine understanding of control systems. Lack of mathematics is part of the problem, for it turns out that simply having a wiring diagram of a control system is not enough to predict even the kind of behavior it will generate, whether stable or unstable or even unpredictably chaotic. The behavior of a control system depends in general on the quantitative values of feedback relationships; and those who have been brought up to think chemically rather than physically, statically rather than dynamically, can find these concepts difficult to come to grips with. For many, homeostasis is synonymous with direct negative feedback with a fixed “set point”; a travesty that has taken root in textbooks and is widely taught to students as the only kind of control system. Then, when other possibilities are stumbled across, they are greeted as amazing novelties instead of the commonplace of classic control theory that they actually are. An example is the recent rise of “allostasis,” that much-promoted but vaguely characterized cluster of concepts that represent nothing that has not always been part of the ordinary conceptual basis of homeostatic control.

Consequently, there is a need to reassert the unitary nature of homeostasis and the variety of forms it can take, so that we are not obliged to reinvent what was common knowledge even 30 years ago, nor to introduce artificial distinctions and boundaries within a field that is in truth perfectly unified. Our students may then once again have the satisfaction of understanding what is, after all, at the very heart of biology, the ultimate reason that organisms exist at all.

The aims in this short review are simple: to set out the main types of control system and their logical relation to one
In the most general case, we want the actual value to be equal to the desired value: the control system is the variable that is being controlled. This is what we teach.

An important concept in control theory is that of the transfer function, which can be thought of as the ratio \( y(t)/x(t) \). Experimentally, the input may often be sinusoidal; the transfer function, which is complex (hence conventionally shown in bold), can then be decomposed into a phase component \( \varphi \) and a gain \( G \). If, as is often the case, we can treat the system as linear, \( T \) is independent of the size of the input, and so are \( G \) and \( \varphi \). For an ideal control system the actual value is at all times equal to the desired value, so \( G = 1 \) and \( \varphi = 0 \) for all frequencies (\( T = 1 \)). In the simplest kind of system, in which \( y \) is literally intended to be constant, we hope that \( G = 1 \), and \( \varphi \) is irrelevant. In general, the aim is to make \( T \) as near unity as possible.

Ballistic control. We need now to look inside the black box and see how it might be implemented. Clearly the plant must have some input capable of influencing its behavior, or the system will be uncontrollable; this signal is called the command. It is clear that the control system’s task is to create commands that will result in the plant generating an output \( y \) that is at all times as close as possible to \( x \).

A very simple way of doing this is shown in Fig. 2. On the right is the plant, whose transfer function \( P \) is given by \( y/c \), and is by definition beyond our power to alter: it is a given. On the left is a device called a controller, whose job is to convert the desired value \( x \) into a suitable command \( c \). Its transfer function \( Q \) is \( c/x \), and is under our control—indeed the job of a control engineer is to see how \( Q \) should be designed to give the best possible performance. We have already seen that “best performance” means that \( T = 1 \); because the transfer function of two systems in series is the product of their individual transfer functions, this means that we want \( PQ = 1 \). This in turn means that the controller should behave like the inverse, or opposite, of the plant: we can write this as \( Q = P^{-1} \). For instance, if (as frequently happens) the gain of the plant falls off at higher frequencies, the gain of the controller should compensate by increasing; if the plant introduces a phase lag, the controller should introduce a phase lead. Thus provided we have perfect information about how the plant behaves, in principle, we can design a perfect controller to match it.

A system of this kind, in which we find out in advance how the plant responds to different commands, and then use this information to select an appropriate command to achieve a particular output, is called a ballistic system. Ballistic means “thrown,” and this is the kind of control system we have to use every time we throw a dart or pitch a ball, or fire a ballistic missile. We calculate in advance what pattern of commands ought to result in the correct result, then issue the commands and hope for the best. Whether we actually achieve our desired result will clearly depend on how thoroughly we understand the plant. Particularly in biological systems, this knowledge can never be exact. Although \( P \) is constant in the short term, in the longer term it cannot be. Growth, disease, fatigue, and age: all may affect what actually happens in response to a given command; and unexpected external factors—a different weight of ball, a cross-wind—may similarly generate noise that will make \( P \) deviate from what had previously been measured. No robust system can possibly work purely ballistically, and all such systems rely on getting information after the event about whether the actual outcome was in fact as intended: a marksman will adjust his sights if the wind is consistently deviating his shots. More formally, what we need to do is continually update the parameters of \( Q \) to make it track the changing \( P \), in the sense of ensuring that the product \( PQ \) is always 1.

Parametric feedforward and feedback. This process of parametric adjustment can occur in two distinct ways. The first deals primarily with noise that—like a cross-wind—arises outside the system. As shown in Fig. 3, what we do is monitor this disturbance, and use this information to adjust the parameters of \( Q \) to allow for it. A good physiological example is the stimulation of insulin release by the taste of food, anticipating that we shall shortly need it. This arrangement (parametric feedforward) has the advantage of forestalling the effect of the disturbance before it actually causes errors, but it relies on extensive knowledge of what disturbances may occur, and precisely how they affect \( P \).

An alternative (Fig. 4) is not to monitor the disturbance, but to monitor its effects; what we do is measure the actual result and subtract it from the desired result to create what is called an error signal. The error signal is a measure of how successful the system has been; ideally, it should be zero. If errors do occur, they can be used to modify the behavior appropriately, and this is called parametric feedback. It has the disadvantage that an error must necessarily occur, but the advantage of not requiring extensive knowledge about the cause of the error.
Humans typically use both methods: an experienced marksman will aim a little upwind, and will also note where the shot actually went and use that information to adjust the next attempt.

**Direct feedback.** Ballistic systems, whether they use parametric adjustment or not, are computationally and informationally demanding because they must be able to recognize threats and to store information about the behavior of the plant. The second major class of control system (the one that is so often used synonymously with homeostasis) is the direct feedback system. As with parametric feedback, this requires the actual output to be compared with the desired output. But instead of using this error signal \((y - x)\) to alter the parameters of the controller, it is used (Fig. 5) as a direct input to the controller, rather than the original \(x\). As a result, the system contains a feedback loop; and because \(y\) is subtracted from \(x\), it is a negative feedback loop. The main advantage of such a system is that \(Q\) can be extremely stupid; in a typical central heating system, for example, \(Q\) simply turns the boiler fully on or fully off, depending on whether the temperature is below or above the set point. The reason that such a crude system works quite well is that the transfer function of the whole system is now not \(PQ\) but \(PQ/(1 + PQ)\). If, as in the central heating system, the gain of \(Q\) is very high, then the gain of the whole expression will tend toward the ideal value of 1.

There is, however, a snag, which has to do with the phase. If the time taken for information to come round the loop is too great, there will be a large phase lag at high frequencies. If this lag reaches 180°, the feedback will be reversed, in effect becoming positive rather than negative. Paradoxically, **too** high a gain will then result in a problem called hunting: the output will swing up and down with ever-increasing amplitude until saturation creates a limit cycle. This is of course exactly what central heating systems actually do, but the resultant oscillations of temperature are tolerable; in the control of the arm, or indeed of many hormones, they would not be.

In some biological cases, the desired input \(x\) is essentially fixed, and does indeed represent a “set point.” But in many other cases, it is not; changes in \(x\) are tracked by changes in \(y\), and the system may then be called a (follow up) servo. This is no great novelty: early 18th-Century windmills were often fitted with fantails, devices that generated an error signal when the direction of the sails did not match that of the wind, which automatically turned the entire mechanism around to face into the wind (12). A classic physiological example of the follow-up servo is the monosynaptic stretch reflex, which to a certain extent can be regarded as translating commands to gamma fibers representing desired muscle length into the force of contraction needed to achieve that length despite the noise represented by changes in load (8).

**Prediction.** The need to eliminate spontaneous oscillation and other kinds of instability dominates the design of feedback control systems. One solution is to construct \(Q\) in such a way as to introduce a phase lead that cancels out the phase lag generated by the loop. This means, in effect, looking at the rate of change of error, or higher derivatives, using information about the past history of the error to predict its future, and thus anticipate what the error will be by the time the command has resulted in a correction of the output. This kind of mechanism was a feature of many anti-aircraft guns used in World War II, which used simple information about rate of change to predict where the target would be by the time the shell reached it. Generating signals that are time derivatives of errors is in effect what many adapting sense organs do—primary afferents from muscle spindles are a good example—and using them in feedback control loops helps stabilize systems that would otherwise be prone to oscillation and other forms of instability. It has been less often described in hormonal control systems, proba-

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**Fig. 3.** A ballistic system with feed forward. External disturbances, or noise, mean that the output \(y\) is not what would be expected for a given command. However, if this noise is monitored, it can be used to modify the command corresponding to a given \(x\), so that the overall transfer function is still satisfactory.

**Fig. 4.** A ballistic system with parametric feedback. Here, noise once again disturbs \(y\), but by itself is monitored and compared with \(x\) to generate an error signal. Persistent errors then result in modification of the controller to ensure \(PQ = 1\).
bly because such systems are generally so sluggish that the gain at around the critical frequency, where the phase of the feedback is inverted, is typically not great enough to cause instability.

Internal feedback. Another solution to the problem of delay in receiving feedback is to predict the actual value not by taking derivatives of the observed error, but by the use of an internal model of the plant (Fig. 6).

In an internal feedback system of this kind, a copy of the command is sent to a model \((P')\) of the actual plant \(P\). If the model is accurate, then its output \(y'\) will exactly match the actual output \(y\); by subtracting \(y'\) from \(x\) we can derive a virtual or predicted error that can then be used in exactly the same way as a real error, as direct feedback to modify the final output \(y\). That this is scarcely a novel idea can be seen from Fig. 7, which shows internal feedback being used as part of the British Admiralty semaphore system in 1825: the signaler winds his handle until he sees a small model of the semaphore arm reach the right position.

The advantage of this roundabout way of doing things is that this predicted error may be available long before there is any information about the actual output, so that many of the problems of instability that are caused by the long phase lags characteristic of biological systems are eliminated. The disadvantage is of course that because it is not a real error, it obviously cannot compensate for unexpected disturbances in the outside world. In the case of the semaphore, were the upper arm to move in the wrong direction or to be driven extremely slowly: visual reaction times are typically of the order of 200 ms. Thus saccades cannot, as one might think, simply be executed by direct feedback, moving the eye until the target is seen to be on the fovea: by the time the information had been received the eye would have hugely overshot. Instead, the saccade is controlled by internal feedback, the superior colliculus in conjunction with the cerebellum providing a virtual stage on which on ongoing saccade is acted out, with the commands to the eye muscles being halted when the virtual target appears to be on the virtual fovea (6, 11). In the longer term, proprioception from the visual system and from the oculomotor muscles corrects this model when its predictions begin to diverge from reality.

It is not difficult to see how a very similar system might for instance be used to control the ingestion of water in response to dehydration. In general, drinking is matched to the body’s need for water, by regulating the point at which drinking, once initiated, is brought to a close. While the urge to drink appears to be driven essentially by error signals relating to cellular dehydration and extracellular fluid volume (10), the cessation of drinking normally occurs well before these basic error signals have been restored to zero (21). It seems highly probable that there is an internal model representing the state of hydration of the body, that is used to predict the effects of any particular pattern of ingestion, and, just as in the case of the saccade, curtails the activity at the point where the model predicts that the need will be met (Fig. 9), an idea incorporated (not always very explicitly) in several early models of the regulation of drinking (13, 17, 25).

Hierarchical control systems. So far, we have progressed from the very simplest kind of ballistic control system, through the prediction \(y'\), which is then used as direct feedback.

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**Fig. 5.** A direct feedback system, or servo. Here the actual output \(y\) is compared with its desired value \(x\) to create an error signal \((y - x)\), which then forms the input of the controller.

**Fig. 6.** Internal feedback using a model of the plant. A copy of the command (efference copy) is sent to an internal model of the plant, \(P'\), whose output is a prediction \(y'\) of the actual output \(y\). This prediction is compared with \(x\) to generate a predicted error, which is then used as direct feedback.
the classic direct negative feedback loop, to the complexities of internal feedback with its models for making predictions of need, and its subsidiary feedback loops to ensure that the controller keeps up with the pace of change of the real world. Real biological control systems often use many of these different strategies in parallel. A good example is the control of muscle length with the help of feedback from muscle spindles. This information, which is partly predictive, is used as direct feedback in the familiar monosynaptic reflex, and as parametric feedback to the cerebellum and elsewhere, to ensure that ballistic programs and models keep pace with the muscle’s actual behavior.

We need finally to consider a further complication, that in biological systems we are seldom faced with the control of a single, isolated variable. More often, there are hierarchies of control: we control muscle length because what we really want to control is arm position; we control arm position because what we really want to do is point a gun; we point the gun because what we really want to do is to stay alive (Fig. 10). Homeostasis means keeping things the same: but not keeping everything the same. There is an intrinsic hierarchy in the body’s parameters, and regulation of the more fundamental ones can be achieved only by deliberately allowing less fundamental ones to vary: to maintain core temperature, for instance, it may often be necessary to sacrifice the well being of the skin.

This idea of hierarchies of homeostats, in which regulatory processes at one level act by altering the set-points of the level below, was discussed in passing by Cannon, and was extensively elaborated and promoted by William Powers more than 30 years ago (18): partly because his work was addressed primarily to psychologists, it is not as well known to physiologists as it should be. If hierarchies of this kind were unbranched, they would not pose much extra conceptual difficulty. But, as Powers pointed out (see, for instance, Ref. 19), in general they are not (Fig. 10). Many muscles around a joint will contribute to joint angle, so that zero joint error may be achieved with various combinations of muscle lengths. To put it another way, the “set points” of these muscles may be altered, depending on what other functions they may be called...
on to perform at the same time (the arm may also be propping us up against a tree). Similarly, there are many combinations of joint positions that will result in the gun being correctly aimed at the target.

Exactly the same situation arises all the time in hormonal systems, often as the result of multiple hormones that have opposing effects on the same system. Calcium homeostasis is a good example, where at first sight it is puzzling that two basic hormones, calcitonin and PTH, are used to regulate the single variable of $[\text{Ca}^{2+}]$. Surely one would be enough? But once it is appreciated that there are at least two aspects of calcium metabolism that must be regulated: on the one hand, plasma $[\text{Ca}^{2+}]$ and on the other, the balance between bone-building and bone-destroying activity, it becomes clear that we have what a mathematician would call a system with two degrees of freedom: provided each hormone has even slightly different effects on the two controlled variables, together they can be used to control them both simultaneously. Another example is the control of acid-base balance, where the two variables to be controlled are, broadly speaking, plasma pH and plasma CO$_2$, and the two command signals are respiratory and renal. The overall “set point” is a position on a two-dimensional plane defined by pH and Pco$_2$, the actual state of the body is in general some other point, and the error is the vector linking the two. Yet another is the control of blood volume and osmolarity (Fig. 11), where there are some sensors such as the hypothalamic receptors for cellular dehydration that in effect monitor one component of the error vector, and others, such as stretch receptors in great veins, that monitor the error vector along a different direction. The renal plant in this case is again twofold, essentially the regulation of urine volume, and the regulation of its concentration. Thinking in this vectorial form can sometimes be helpful in trying to understand the control relationships involved (3).

In any such system, it is inevitable that the set point for one subsystem must necessarily depend on the operation of the other. If we are hyperventilating as a consequence of metabolic acidosis, inevitably there will be fall in Pco$_2$. In a hierarchical system, subordinate set points will be changing all the time to reflect the needs of systems that are hierarchically above them, and some of these changes may reflect anticipatory responses from model systems, as for instance when blood flow to muscles increases in advance of exercise. Thus blood pressure is regulated to a set point, which itself is subject to alteration in different circumstances, an observation that has sometimes been used to promote the idea that the control of blood pressure is regulated not homeostatically but “allostatically” (24). Yet the notion of sympathetic regulation of this set point had already been explicitly included by Cannon in 1932 in what he considered to be homeostasis. Nested homeostasis is in fact implied whenever the so-called set point is subject to alteration, an ancient concept exemplified for instance by the adjustable gun sights of rifles and artillery.

**Ultrastability.** Another situation in which a change of set point may be required is when a sudden change in the outside world demands a degree of parametric feedback that is so radical as to amount to remodeling. As Kenneth Craik realized some 60 years ago (although his thoughts remained unpublished for over 20 years; see Ref. 7), control systems must be
capable of radically reorganizing themselves in response to long-term changes in circumstance, something Ross Ashby later (1) called ultrastability, the ability to maintain homeostasis not by local hill climbing, small incremental changes in the model’s parameters, but by a sort of leap to a neighboring peak. Ross-Ashby’s homeostats, experimental electromechanical models that acted co-operatively to settle down in response to environmental change imposed by the experimenter, were also fitted with a mechanism by which prolonged inability to find equilibrium resulted in random rewiring, this being repeated until a configuration was finally achieved that permitted stable homeostasis in the changed circumstances (Craik probably also built such devices himself). That survival may mean redefining the organism itself is of course the fundamental paradox of biology that underpins the entire reproductive process. This was an idea already current in some of the writings of R. A. Fisher, in which he anticipated much of what later became known as “game theory” (9). Recent work (5) on reaction times has suggested an analogous mechanism by which a random element is “deliberately” injected into our responses, ensuring that we do not always mechanically do exactly the same thing in identical circumstances, resulting occasionally in mold-breaking behavior capable of finding new solutions when faced with environmental instability.

Finally, but still within the confines of classical control theory, for a motile organism homeostasis is frequently achieved not so much by adapting to an environment, as moving to a better one. Homeostatic regulation is a combination of direct monitoring and modification of the milieu intérieur, and indirect control through prediction of errors by use of the special senses, and through external homeostasis achieved by movement and consummation. When we are cold, we increase our metabolism and reduce heat exchange through the skin by vasoconstriction; but we also put on more clothes and move nearer the fire. The role of the hypothalamus in all this is pivotal. On the input side (Fig. 12) it is provided with predictive information about future threats by neural sensory systems, and through autonomic afferents and more directly by its

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**Fig. 11.** A C plot showing extracellular fluid (ECF) volume (x-axis) and intracellular fluid volume (ICF) or plasma osmolality (y-axis). The desired value, x, is shown at the center; at any moment the two actual values will be different (y): (y = x) represents the error vector. Various procedures (ingestion or loss of water, salt, or isotonic saline) will move the output in the directions shown. Thus by appropriate combinations of them, y can be brought back to the set point (see Ref. 3).

**Fig. 12.** Glucostasis: the hypothalamus as the ultimate controller. Direct feedback information is available from its own glucose-monitoring receptors; in addition, it has predictive feedforward information from the autonomic nervous system (ANS) and indirectly from the special senses. On the output side, it acts partly through controlling the release of particular glucostatic hormones (GH), and partly through the control of behavior, either internally, as in the case of salivation, or externally through predatory behavior and eating, which rely on internal models of the likely consequences of such activity. Figure adapted from Ref. 6.
our relatively detailed quantitative knowledge of neural control systems, seeking out parallels through which types of control, and the close relationship between neural and hormonal control systems may be used to advance our understanding of the long-term homeostasis of the body as a whole.

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