NANCY ROTHWELL

Homeostasis

Animals are able to maintain a constant internal environment despite wide variations in external conditions. How is this achieved?

On a cold winter morning, getting out of your warm bed can be an unpleasant experience. Then, just after getting warm, you venture outside where the temperature may be below freezing. Just in these normal activities your body can be exposed to a range of external temperatures of over 20°C. Yet the temperature of the brain is unlikely to vary by much more than 0.1°C. Other homeotherms, which lack the benefits of clothing or central heating, also maintain a remarkably constant core body temperature, sometimes in environments ranging in temperature by more than 40°C. Homeothermy (the ability to maintain constant internal body temperature) is an excellent example of **homeostasis**, whereby the internal environment of an organism is maintained quite constant, in spite of marked external variations and continuous challenges.

WHAT IS HOMEOSTASIS?

Homeostasis literally means 'same condition', and is fundamental to our understanding of biological processes, because it is essential for survival. The first person to realise the importance of homeostasis was the French scientist, Claude Bernard. During the early eighteenth century Bernard was struggling to understand how animals can live in such rapidly changing conditions. Eventually he realised that survival depends on maintaining the **internal environment** of the body quite constant by making rapid adjustments in response to external and internal changes and requirements. He termed this internal environment within an organism the *'interier milieu'*, and Bernard's basic principles of homeostasis still hold true today.

Homeostasis is not simply a feature of mammals, but is essential for almost all organisms. In poikilotherms, such as reptiles, amphibians and fish, the body temperature drifts with the environmental temperature. These animals suffer the consequences of a low body temperature — they are sluggish in the cold. However, they do regulate many other physiological factors. Even simple organisms such as bacteria regulate their interior environment by mechanisms not too different from those in higher animals. They sense changes and make the necessary adaptations and adjustments.

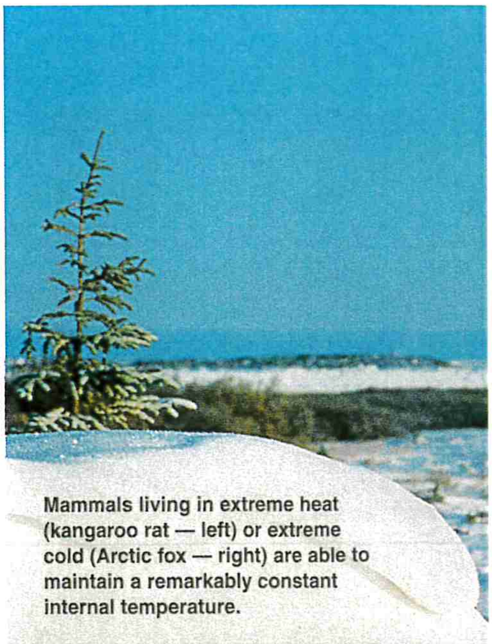
WHY IS HOMEOSTASIS IMPORTANT?

Regulating factors such as temperature, pH or glucose concentration is costly. It requires considerable amounts of energy and complex mechanisms to keep these functions within defined limits — so why bother? As for most biological functions, very efficient systems have evolved, which are dependent on basic physical and chemical principles of the environment in which we live. Most chemical reactions have an optimal activity — that is, they work best under specific conditions. Enzymes, for example, the very basis of all biological processes, are most active at specific temperatures and pH. In most organisms enzymes are most active at the regulated body temperature and pH. A change in conditions means a dramatic loss of efficiency, so survival chances are greatest when these conditions are maintained.

HOW IS HOMEOSTASIS ACHIEVED?

Maintenance of a constant internal environment can be achieved by individual cells, tissues, organs or by the whole organism. Cells from both simple and complex organisms can regulate intracellular pH, glucose and oxygen supply, and repair essential components. Some of this 'apparent' regulation is the result of simple chemical reactions, such as buffers regulating pH, or changes in the rate of use of glucose or oxygen, depending on availability.

Within tissues there are many cases of regulation. Local blood flow can be regulated by the activity of the tissues, which in turn determines the levels of oxygen and glucose needed, carbon dioxide production and pH. This in turn changes flow to the tissues to meet the altered demand. This phenomenon, known as autoregulation, is particularly important in the brain.



Mammals living in extreme heat (kangaroo rat — left) or extreme cold (Arctic fox — right) are able to maintain a remarkably constant internal temperature.

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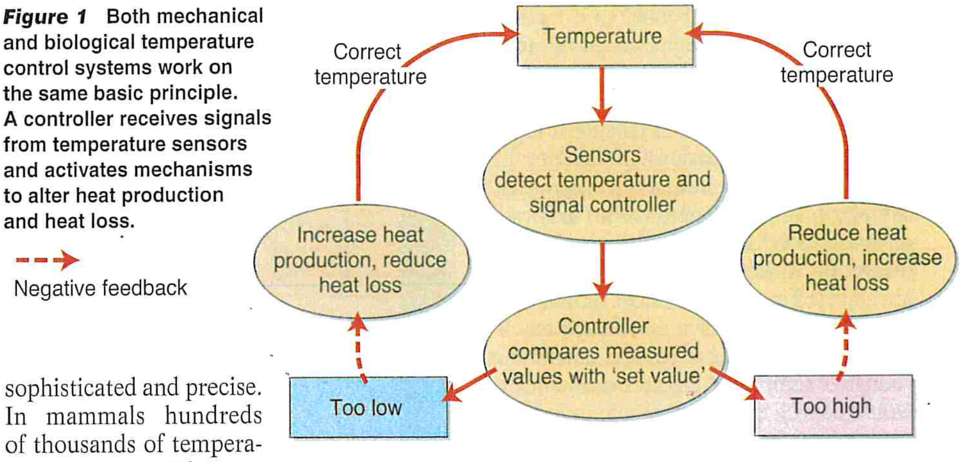
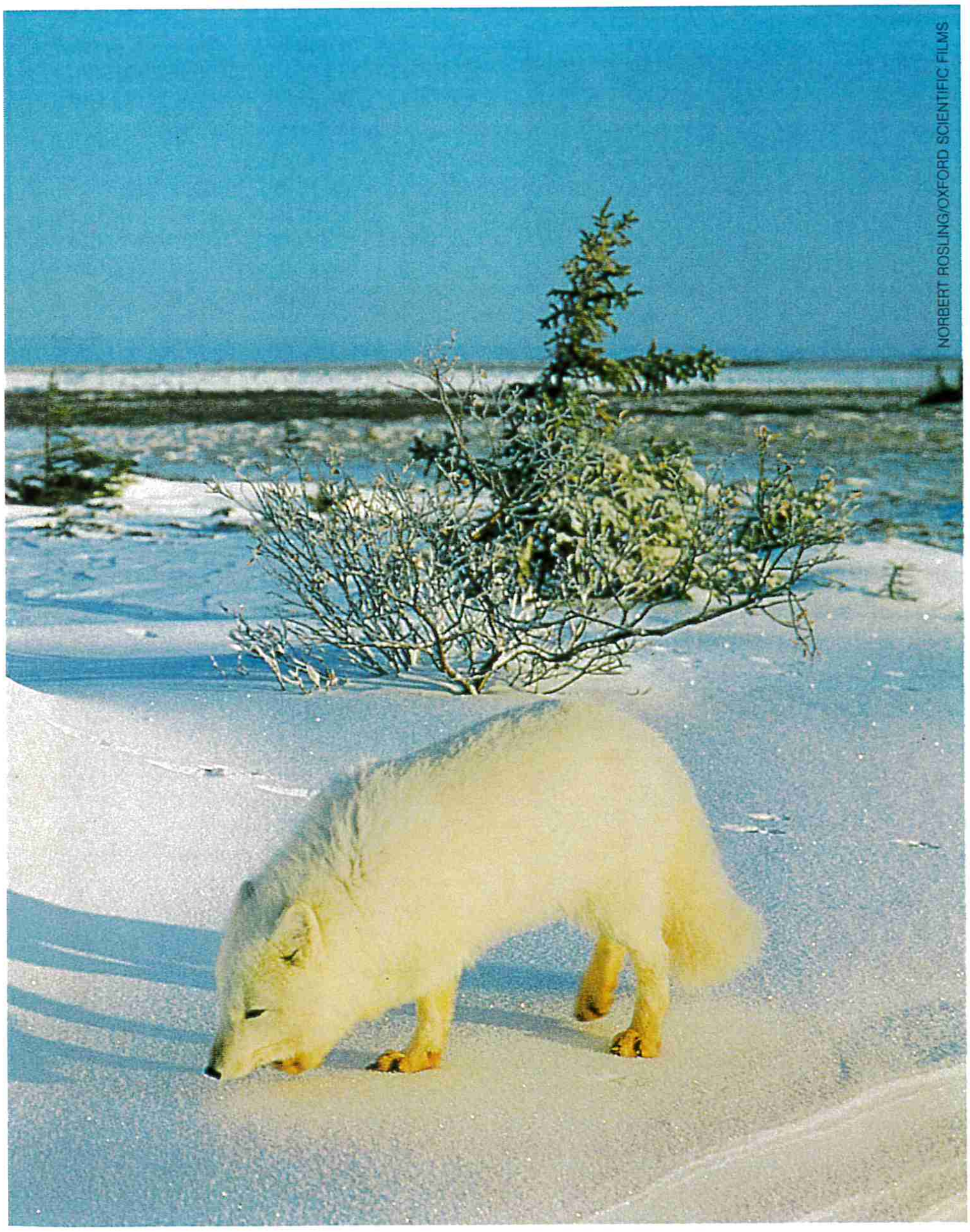
More complex functions in higher animals are regulated by the brain, which integrates an elaborate array of signals from different parts of the body. An excellent example of this is the one we began with — temperature regulation in homeotherms, such as humans. At a simplistic level this can be compared to a central heating system (which in warm climates may include air conditioning) in a room or building. Here, as in homeostasis, the central system tries to keep temperature constant (see Figure 1). The defined temperature of the room or building is **set** at the determined level that is most comfortable, perhaps 18°C in a working area. Sensors in the room detect if the temperature of the room is too low and send a signal to switch the heating on, or if the temperature is too high the heating is turned off or the air conditioning activated. In this way the temperature can be kept quite constant.

Homeothermy is based on the same principle, but is much more complex, sophisticated and precise. In mammals hundreds of thousands of temperature receptors (thermoreceptors), located all over the body, send signals to the brain. Some of these are located in the skin to sense the external environment (to provide an alarm as to when the body may cool down); others reside throughout the major organs, particularly those most likely to be disrupted by changes in temperature, such as the brain or heart. These thermoreceptors send electrical signals to a part of the brain known as the **hypothalamus**. It is here that the set or preferred temperature is believed to reside, and where specific neurones (brain nerve cells) are highly sensitive to temperature.

Figure 1 **Both mechanical and biological temperature control systems work on the same basic principle. A controller receives signals from temperature sensors and activates mechanisms to alter heat production and heat loss.**





Most cells in the body approximately double their activity when temperature is increased by 10°C. Specific neurones in the hypothalamus respond to changes in temperature of fractions of a degree Celsius, and also receive inputs from sensors elsewhere in the body. If these signals indicate that body temperature is too low, the hypothalamus will activate processes to increase heat production (e.g. by shivering) and to reduce heat loss (e.g. piloerection to lift fur or hair and increase insulation, and vasoconstriction to reduce blood flow to the skin and extremities). Conversely, if body temperature starts to rise, blood flow will increase in the skin (vasodilation), causing greater heat loss and, if necessary, sweating will increase heat loss through evaporation.

Thus, temperature regulation in homeotherms and the central heating system in a building both depend on the phenomenon of **negative feedback**, which is important throughout the physical and biological world and is a key feature of homeostasis. If the heating raises the temperature too much, sensors send a **negative** signal to switch it off.

REGULATION BY THE BRAIN

Many physiological functions are regulated by the brain, and the hypothalamus is particularly important in homeostasis. It is the main site for integration of signals involved in the control of blood glucose, appetite and feeding, body mass, temperature, drinking, sexual behaviour and an array of hormonal changes. The hypothalamus is referred to as an 'old' part of the brain, since it is present in many lower species, but it can be influenced by 'higher' brain centres. So, for example, many animals use complex behaviours to regulate temperature, such as huddling, nest building or wearing clothing, and control of feeding behaviour can easily be overridden by the sight, taste and smell of food.

Signals to (**afferent**) and from (**efferent**) the brain can be by nerves (the most rapid form of communication), hormones or physical factors, such as temperature, osmolarity or pH changes within the brain or in the blood supplied to the brain. The means by which physiological functions are adjusted in order to restore or maintain homeostasis are known as **effector mechanisms** because they effect (i.e. **cause**) the change. Examples of effector mechanisms would be a change in heart rate or cardiac output required to increase blood flow during exercise, or the changes in heat production and heat loss, which allow body temperature to be maintained at a constant level.

Many of these effector processes are controlled by the **autonomic nervous system** (see BIOLOGICAL SCIENCES REVIEW, Vol. 11, No. 4, pp. 30–34) — the part of the nervous system that is not under conscious control, but is critical to survival and maintenance of homeostasis. The autonomic nervous system, which regulates functions such as heart rate, breathing, digestion, metabolism, blood flow and many other functions, has two branches — the sympathetic nervous system and the parasympathetic nervous system (see Figure 2).

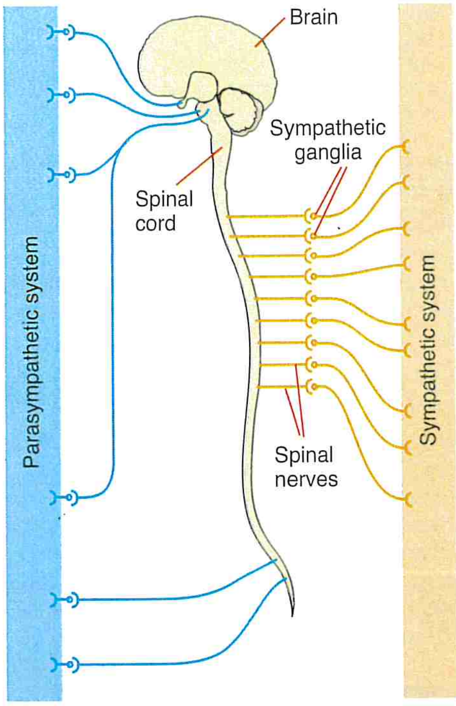


Figure 2 **The parasympathetic nerves of the autonomic nervous system originate from the lower brain and sacral (lower) part of the spinal cord. Those of the sympathetic system originate in the thoracic and lumbar (middle) part of the cord. Both carry signals from the brain to tissues throughout the body.**

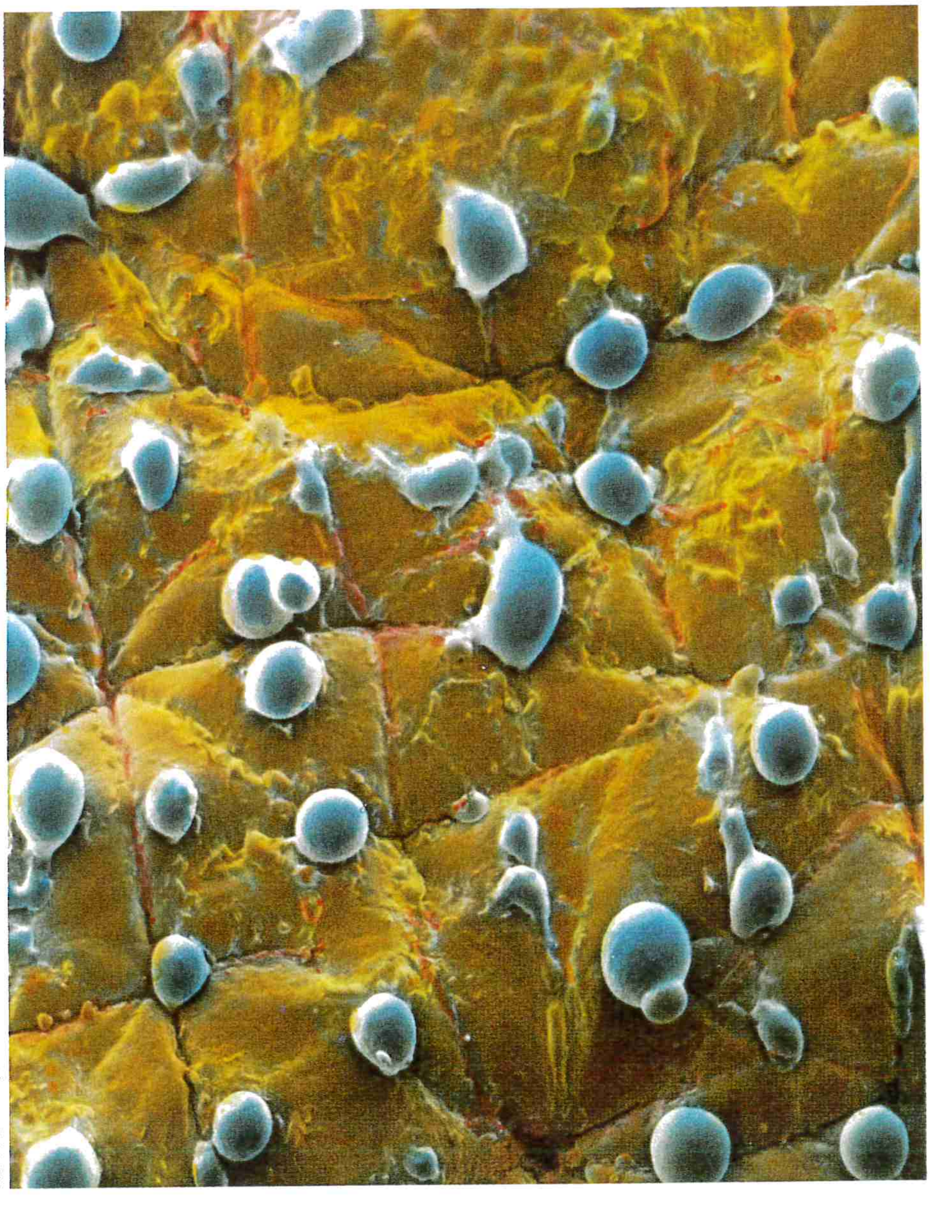
The sympathetic nervous system is generally 'activating'. It stimulates heart rate, heat production, release of fuel from stores (e.g. glucose from glycogen, and fatty acids from lipids in adipose tissue and muscle). Its effects are most noticeable during the 'fight or flight' response, for example just as you are about to take an exam or before a big race.

The parasympathetic nervous system slows down the heart, and is important in controlling digestion and absorption of nutrients. It will be most active when you are warm, comfortable and resting after a large meal.

A vast array of hormones also regulate physiological processes and maintain homeostasis, and many of these are controlled by 'releasing factors' produced in the hypothalamus. These releasing factors are peptides which stimulate or inhibit the release of hormones from endocrine organs. So, for example, during stress the sympathetic nervous system will be activated, but the hypothalamus also produces a peptide called corticotrophin releasing factor (CRF). CRF travels via the blood to the pituitary gland to cause release of adrenocorticotrophic hormone (ACTH), which in turn acts on the adrenal gland to cause production and release of cortisol — another very important hormone involved in responses to stress and disease (see Figure 3).

CONSTANT OR VARIABLE?

Human core body temperature rarely changes by more than a degree or so. It falls slightly during sleep and may rise during severe exercise, but any greater changes indicate disease (usually infection) — what we call fever. Similarly, pH, blood and tissue oxygen and carbon dioxide concentrations and osmolarity must stay within narrow limits for survival. However, many other functions are not regulated so precisely. Body



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False-colour scanning electron micrograph of the back of the human hand. The blue droplets are sweat, emerging from sweat glands — one of the ways in which the body is able to lose heat. (× 50)

mass and fat stores, for example, change during growth, pregnancy and lactation.

Of course, a large number of humans and domesticated animals lay down excess fat and become obese, suggesting that body mass and energy stores are not well regulated. Nevertheless, studies on animals and humans have shown that many will spontaneously return to exactly the same mass after a period of overeating and fat accumulation or after a loss in body mass.

Recent discoveries have identified a hormone known as leptin, which is produced by adipose tissue (where fat is stored). When fat stores increase, more leptin is produced and this signals the hypothalamus to switch off feeding and turn up metabolism, which should then reduce fat stores. This is another example of negative feedback. Obesity may be due to poor responsiveness of the hypothalamus to leptin, or the fact that higher brain regions simply override the normal regulation because of the pleasurable effects of food!

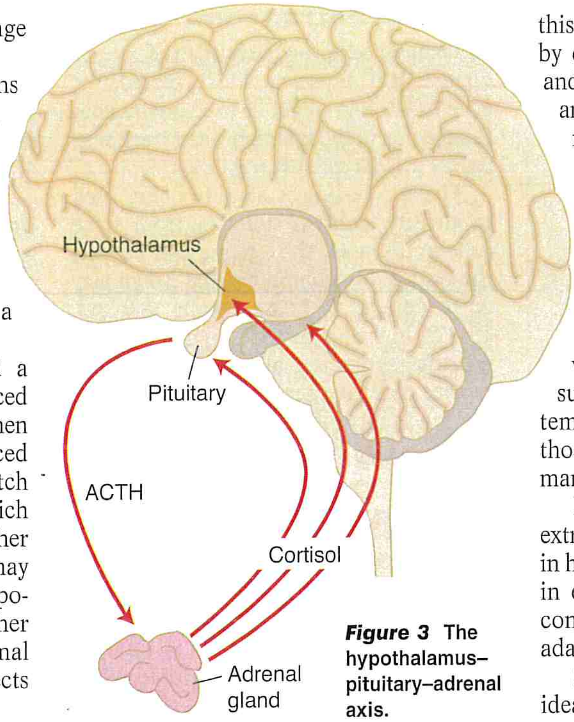


Figure 3 **The hypothalamus–pituitary–adrenal axis.**

HOMEOSTASIS IN EXTREME CONDITIONS

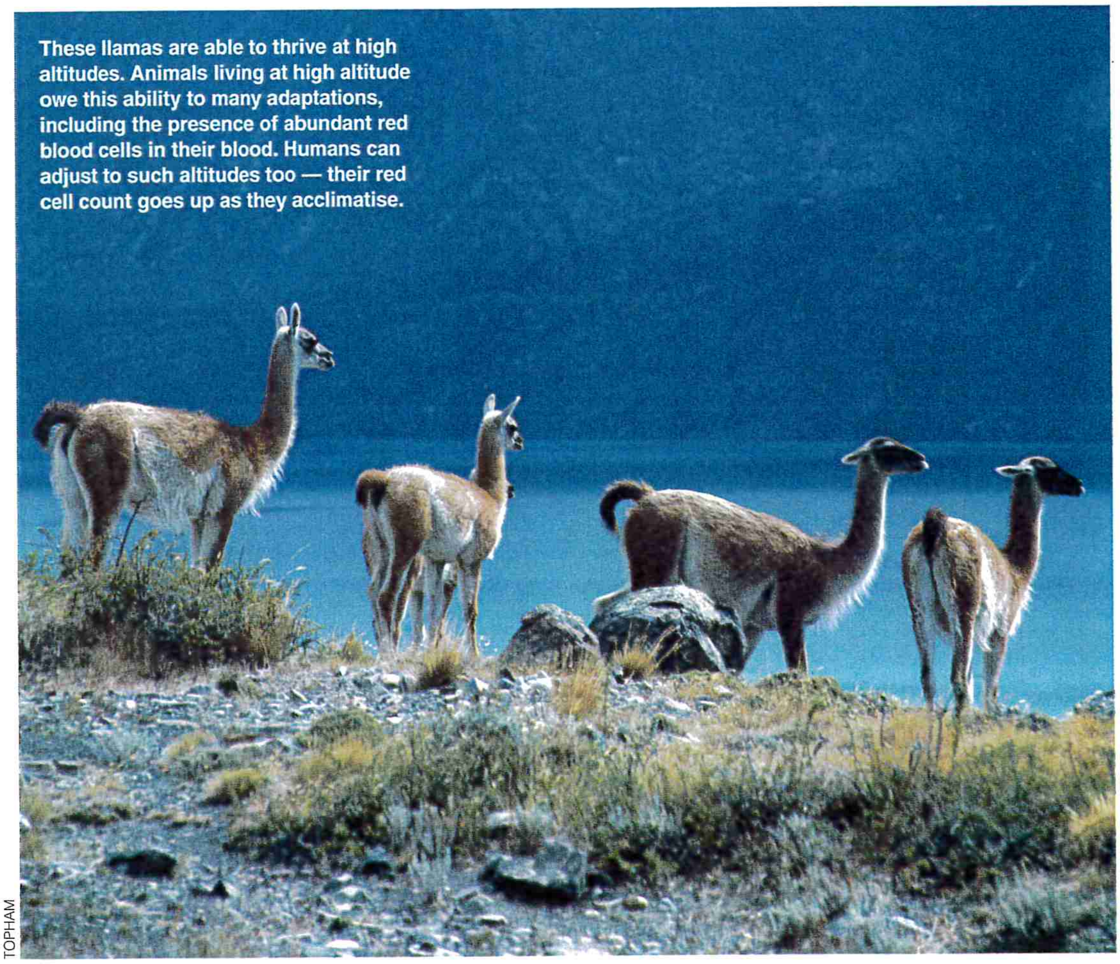
Some of the most fascinating aspects of homeostasis can be seen in animals that have adapted to extreme environments. Many are able to survive in conditions of severe cold or heat by developing specialist forms of temperature regulation. Examples include very effective insulation in polar animals or large ears and long legs to increase heat loss in the tropics. Some animals, such as hibernators, seem to 'opt out' of homeothermy, allowing their temperature to fall and, in this way, save food. They survive the winter by dropping their heart rates, respiration and metabolism to remarkably low levels, and therefore reduce the amount of energy needed to survive.

Mammals living at high altitude where oxygen is scarce (such as llamas and Peruvian Indians) have more red blood cells, each with more haemoglobin to deliver oxygen more efficiently than those at sea level.

Desert animals, such as gerbils, use water and food very efficiently and some, such as many gazelles, can withstand body temperatures several degrees higher than those that would prove fatal for most other mammals.

Lower organisms can live in even more extreme environments. Bacteria can be found in hot springs at temperatures above 100°C, in extremes of pH and in very high salt conditions, again because of remarkable adaptations.

So while Claude Bernard had the right idea about 'the fixity of the internal environment', we now know that homeostasis is much more complex. Some aspects of the internal environment remain remarkably constant, while others vary considerably, but usually return to the original (or similar) level after a disruption. This is achieved by a fascinating array of different mechanisms and intriguing adaptations, because failure of homeostasis is usually fatal. ■



These llamas are able to thrive at high altitudes. Animals living at high altitude owe this ability to many adaptations, including the presence of abundant red blood cells in their blood. Humans can adjust to such altitudes too — their red cell count goes up as they acclimatise.

TOPHAM

THINGS TO DO

Homeostasis was the subject of the Royal Institution Christmas Lectures given by Nancy Rothwell in 1998 ('Staying alive: the body in balance') and televised by the BBC. Videos of the five lectures and an accompanying booklet can be obtained from: BBC Videos, 80 Wood Lane, London W12 0TT. Tel: 0181 576 3104. Fax: 0181 576 2916.

Nancy Rothwell is Professor of Physiology in the School of Biological Sciences at the University of Manchester. Her main research focuses on trying to understand how the brain controls responses to disease and injury and the causes of damage to the brain after stroke and injury. For further details see

http://www.biomed.man.ac.uk