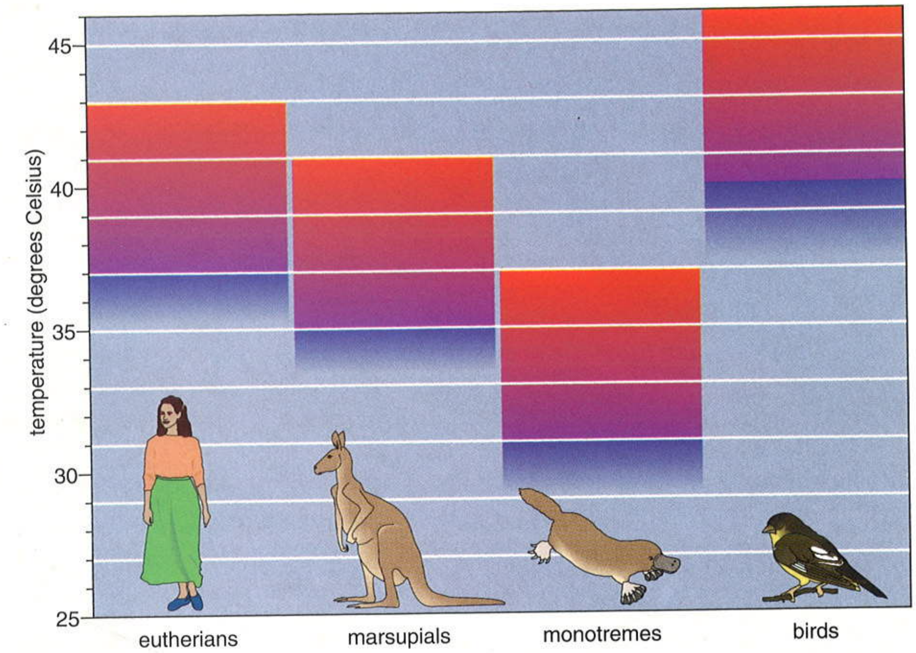

Figure 5. Body temperature differs in different groups of animals. Eutherian mammals, which include humans, have a normal body temperature *(dark blue)* of about 37 degrees Celsius and a lethal body temperature *(red)* of about 43 degrees Celsius. Marsupials, such as kangaroos, have a normal temperature of about 35 degrees and a lethal temperature of about 41 degrees. Monotremes, such as a platypus, have a normal temperature of about 31 degrees and a lethal temperature of about 37 degrees. Birds have a normal temperature around 40 degrees and a lethal temperature around 46 degrees. It remains unclear why different orders have different normal temperatures, or how they "know" what temperature to maintain. Nevertheless, the difference between normal and lethal temperatures is uniformly about six degrees for each of these groups.

G. C. Kelley (Photo Researchers, Inc.)

Figure 6. Desert iguana seeks a warmer environment when infected with bacterial pyrogens, fever-causing compounds. Under normal conditions, a desert iguana prefers to stay in an area that maintains its body temperature at about 38 degrees Celsius. When infected with pyrogens, however, an iguana prefers an environment that increases its body temperature to about 40 degrees Celsius.

did we interfere with the body's natural defense mechanisms?

The question is not easily answered in experiments with our usual laboratory animals. Say that we infect a group of rats with a suitable pathogen and administer aspirin to one-half of them. If the rats that receive aspirin do better, we do not know whether this is because their fever was reduced or because aspirin has other beneficial effects.

An interesting answer to this question was devised by Matthew Kluger at the University of Michigan. Instead of studying a warm-blooded animal, he chose a lizard, the desert iguana. When these animals are placed in an environment where they can select a range of temperatures, they prefer to stay where their body temperature remains at about 38 degrees Celsius. If the lizards are infected with a suitable pathogen, they select an environment where their body temperature is elevated by two degrees above their usual preferred temperature.

In 1975 Kluger tested the value of the higher body temperature. Instead of providing the animals with a choice, he kept one group of infected lizards at their normally preferred temperature of 38 degrees Celsius and another group at the "fever" temperature of 40 degrees. The survival rate of the animals at the higher temperature was significantly better. Since only the animals' body temperatures were different, the inescapable conclusion is that the higher body temperature aided in combating the bacterial infection.

Although the elevated set point for body temperature caused by microbial toxins can be perceived as a mechanism helpful to combat disease, we fail to understand the mechanism that causes the change in the cells of the temperature-regulation center. Nevertheless, to the comparative physiologist it is interesting that the value of an increased body temperature was demonstrated in a cold-blooded animal, and not in one of the usual warm-blooded laboratory mammals that serve as models in so much physiological research.

The Body Temperature of Camels

It is convenient to accept the concept of a set point for body temperature, in spite of the regular diurnal variations of a couple of degrees. But consider the body temperature of camels. A well-fed and fully hydrated camel has regular diurnal fluctuations in body temperature of about two degrees Celsius, like other eutherian mammals. But when a camel is deprived of drinking water and becomes increasingly dehydrated under hot desert conditions, the diurnal fluctuations increase to as much as seven degrees, from a low of 34 degrees Celsius to a maximum of 41 degrees Celsius. These fluctuations are well regulated and the upper limit of 41 degrees is defended against a further rise by increased evaporation and sweating.

Maintaining an elevated body temperature during severe heat has obvious advantages in water conservation. The gradual rise in body temperature during a hot day means that heat is stored in the camel's body, to be dissipated without the use of water in the cooler night. A second important factor is that it takes less water to maintain the body at 41 degrees than to keep it at a lower 37 degrees, which would require a much higher rate of evaporation. These advantages to the water economy are obvious, but they leave open the question of how the change in the control mechanism is achieved.

We know that the mechanism through which body temperature is maintained is located in the hypothalamic area of the brain, but we do not know why body temperature is maintained at a given level and, in particular, how the cells of the control center receive their instructions about which level is to be maintained. In the case of the camel, we know how these centers are affected by increasing dehydration, and we know that the effect is advantageous to the animal, but we know nothing about how the changes are achieved.

We have to answer questions such as: What genetic mechanisms are responsible, not only for the normal set point for body temperature but also for the carefully regulated changes in set points and diurnal cycles that operate in the intact living organism? We know the proximal mechanism of temperature regulation, but not the program that directs and controls the operation of the mechanisms.

Fundamental Questions of Control

In general, all living organisms maintain a relatively steady state and have elaborate mechanisms to resist changes and maintain constant conditions. The regulatory mechanisms involved in the maintenance of steady-state conditions and in the responses to short-term changes are reasonably well understood. Consider, for example, the well-known effects of exercise on the regulation of respiration, heart rate, body temperature and so on.

The regulation of long-term changes, however, is less well understood. For example, consider the ability of the liver to regenerate. A mammal tolerates surgical removal of a large portion of the liver. The remaining liver begins to regenerate to make up for the lost tissue. The growth of new liver tissue continues until the liver reaches its original size, and then it ceases. Little is known about the signals that initiate the regeneration, except that certain growth-promoting substances are involved, but the signals that make the growth cease when the liver reaches the "correct" size remain obscure.

During the period of regeneration, the liver must produce the proteins needed for its own growth. In addition, it must compensate for the depletion of plasma proteins that follows partial hepatectomy. Confronted with this dilemma, the liver gives preference to the syn-

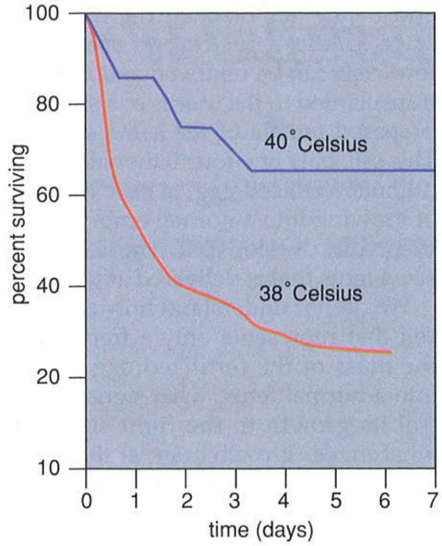

Figure 7. Fever is a defensive mechanism. Matthew Kluger and his colleagues infected two groups of desert iguanas with fever-causing bacteria, and then placed the iguanas in environments that kept their body temperatures at 38 or 40 degrees Celsius. The percentage of surviving iguanas was significantly higher for the group kept at 40 degrees Celsius compared with the group kept at 38 degrees. These results indicate that a higher body temperature helps an iguana fight the pathogen. (Adapted from Kluger et al 1975.)

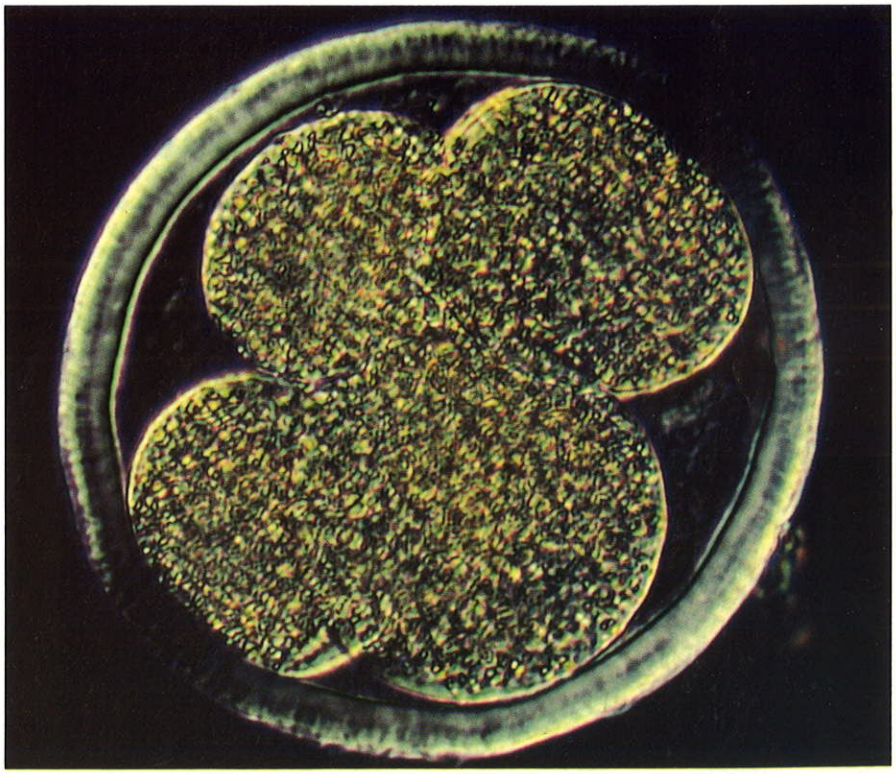

Figure 8. Single cell from four-cell-stage fertilized cow egg can produce a normal embryo. The mechanisms that allow a fraction of an egg's mass to produce a normal full-sized embryo are unknown. Many of the steps behind steady-state regulation are known, such as the control of body temperature. The mechanisms of long-term regulation, such embryonic development, are less well known. Nevertheless, we cannot answer the ultimate question: How does an organism select the "proper" set points? (Photograph courtesy of George Seidel.)

thesis of cellular proteins, and only after a substantial amount of liver has been regenerated does the liver turn to producing plasma proteins. The conclusion of these studies was that the kind of protein synthesized is controlled by bodily demands. The question remains: What is a "bodily demand" and how is it discovered and communicated so that it induces appropriate responses in the regenerating liver?

Many related problems concern other areas of the growth and development of an organism. For example, the normal growth of a human infant depends on the release of growth hormone from the pituitary gland. The sudden spurt in the growth of a human male in early puberty is initiated by the effect that gonadal hormones, such as testosterone, have on the production of growth hormone, but we have no clear understanding of what regulates this increase in production of male hormone and makes growth cease when the body reaches the "correct" size.

Consider a fertilized mammalian egg that has undergone two divisions and hence has reached the four-cell stage. Under a microscope one of the four cells can be removed and then be transplanted to the uterus of a suitably prepared female of the same species. This cell, only one-fourth the size of the original fertilized egg, is now capable of growing into a normal embryo that eventually develops into a normal, full-sized fetus that is delivered at term.

We do not understand how a single cell that represents only a fraction of the mass of the fertilized egg grows into a normal fetus, what signals control its growth to the right size and what makes growth cease at the exact correct size. How does the organism "know" what its right size is?

Closing the Circle

Our knowledge is still inadequate, and the many unsolved problems are uppermost in the minds of those of us who are concerned with how the integrated organism functions.

We must remember that the immense progress in molecular biology during the past half-century, in the end must be referred back to what it all means for the complete, living, functioning organism. When eventually all the exciting progress in molecular biology has come together in a coherent picture, we will have come full circle and will have returned to the unsolved problems of how the intact, living organism works.

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