How Are Control Systems Controlled?

We understand many of the mechanisms that control animal functions, but exactly how these mechanisms are governed remains obscure

Knut Schmidt-Nielsen

Why do moose on a large island in Lake Superior wade into the water to graze on aquatic plants? Why do cows in South Africa show a craving for chewing old bones? What does the odd behavior of animals reveal about the mechanisms that regulate their ability to maintain internal steady states?

In this article, I shall describe some fascinating studies that provide answers to such questions but that nevertheless raise new problems to which we do not have adequate answers.

The moose that live on Isle Royale in Lake Superior are confined to the island, and it is therefore possible to evaluate accurately their nutritional status based on the food available to them. The vegetation that these large ruminants browse on has a very low sodium content—so low that it supplies only about one-tenth of the animals' sodium requirement.

On this diet the animals should be severely sodium deficient and unable either to maintain themselves or to reproduce. Nevertheless, the moose show no overt signs of sodium deficiency, and each year they produce normal calves. The solution to this puzzle was found by Daniel Botkin and his colleagues at Yale University.

During about eight weeks in summer, Botkin's group found, the moose feed on submerged and floating aquatic plants that have a sodium content 50 to 500 times higher than the island's terrestrial plants. The sodium intake from the aquatic vegetation replenishes the animals' sodium resources, bringing their yearly intake up to the level needed for maintenance and reproduction. The sodium ingested in summer is stored in the large volume of fluid in the rumen (the large storage chamber in the stomach of ruminants such as cattle, deer and sheep) and probably also in the bones of the skeletal system.

In general, the saliva of ruminants is a solution consisting mostly of sodium bicarbonate, and it is known from studies by Derek Denton of the University of Melbourne that if sheep are deficient in sodium, the sodium in the saliva is replaced by potassium. Since saliva is the main source of the rumen fluids, sodium-deficient animals have potassium as the primary cation in the rumen fluid. When sodium is again available—as it is when the moose eat aquatic plants—saliva and rumen return to containing primarily sodium, and the rumen now provides a large reserve of sodium that evidently is sufficient for the year's needs. It therefore seems clear that the feeding on aquatic plants in summer is related to the animals' needs and their appetite for sodium.

The salt appetite of ruminants is familiar to us, and because it is important in animal husbandry it has been widely studied. An elegant method to produce sodium deficiency in sheep was devised by Derek Denton. He exteriorized the duct from one of the parotid glands, so that a daily amount of several liters of sodium-containing saliva could be drained off, rapidly rendering the animal severely sodium deficient.

This procedure permitted the study of sodium appetite. When offered a choice of water and solutions of sodium bicarbonate, sodium-deficient sheep voluntarily drank sodium-bicarbonate solutions in amounts appropriate to compensate for the sodium loss.

We know that the physiological mechanisms responsible for the sodium appetite depend on a center in the brain that responds to the sodium concentration of the extracellular fluid. We know that a deviation from the desired level causes a response, but we do not understand how the cells in the controlling center "know" what the desired level is, and how the deviations are translated into a precise response of the whole organism. What we do know, then, is what ultimate mechanism sets the correct and proper level.

Chewing Bones

Let me mention another example of behavior governed by a physiological deficiency. In the 1920s the South African investigator Henry Green reported on the penchant of cattle for chewing on old bones from dead animals. Although the preference was for old, bleached bones, the craving for bone could be so strong that cattle would attack partly decomposed carcasses and occasionally die from botulism.

Green showed that the behavior was related to a widespread phosphate deficiency in the local soil, and that supplying adequate amounts of phosphate eliminated the ingestion of bone. The propensity for gnawing and ingestion of bones, osteophagia, is a well-known veterinary problem, not only in South Africa but also in many other phosphate-deficient areas of the world, such as Argentina, Australia and the United States.

The phenomenon of osteophagia has been studied in Australia by Denton

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Dean Krakel II (Photo Researchers, Inc.)

Figure 1. Moose on Isle Royale in Lake Superior face a potential sodium deficiency. The terrestrial vegetation on the island provides less than one-tenth of the animals' sodium requirement. Nevertheless, the moose are not sodium deficient. For eight weeks each summer, the moose enhance their sodium intake by eating aquatic vegetation, which is high in sodium. The summer sodium intake suffices for the entire year.

and his collaborators. Because saliva contains some phosphate, in addition to sodium bicarbonate, cattle can be made phosphate deficient by Denton's saliva-draining technique. To avoid sodium deficiency when large volumes of saliva were drained off, Denton added sodium bicarbonate to the drinking water. Cows that were made phosphate deficient in this way rapidly showed an avid interest in chewing on bones.

The behavior was clearly related to phosphate deficiency, for an intravenous infusion of buffered sodium phosphate abolishes bone appetite within a fraction of an hour. If the infusion was discontinued, the plasma phosphate gradually declined, and within hours the appetite for bones returned.

Phosphate deficiency is not unique to cattle. Reindeer carry large antlers, which have a composition similar to bone, or calcium phosphate. These large structures are shed each year and must be replaced, both in males and females. Likewise, giraffes that live on the phosphate-deficient soils in East Africa seek the same kind of supplement to satisfy their craving for phosphate.

The behavior is elicited by olfactory stimuli. Meat, blood and fat are not attractive to phosphate-deficient cows, but bones are, and more so after the bones have aged for several years. The attractant is an organic constituent that disappears if the bone is heated to 500 degrees Celsius. Ashed bones are not attractive, but the addition of extracts from unheated bone renders them attractive to phosphate-deficient cows.

In both sodium and phosphate deficiency, the animal's behavior serves to correct a physiological imbalance or deficiency. Since the behavior requires no learning process, the response reveals a genetic programming of ingestive behavior. Even if one day we are able to pinpoint the particular neurons that serve to correct a given imbalance, the next question is: What mechanism makes these neurons "know" the particular level or set point that the organism aims to reach?

Regulating Water

Many other physiological regulatory mechanisms and how they operate are familiar to us. Half a century ago E. B. Verney of the University of Cambridge found that when water is given to a

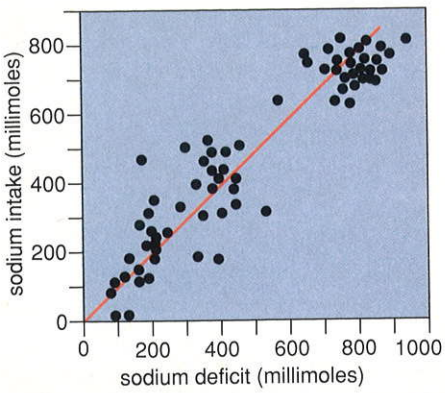


Figure 2. Sheep can be made sodium deficient by draining saliva from a parotid gland. When the sodium-deficient sheep are then offered a solution of sodium bicarbonate, they drink enough (*y*-axis) to offset their sodium loss (*x*-axis), as shown in this regression line *(red)*. (Data from Derek Denton.)

dog, there is a 15-minute delay between the peak water load and the maximum rate of water excretion. Verney introduced the term osmoreceptor for the nerve cells in the brain that respond to the water load, and he showed them to be responsible for control of the secretion of the antidiuretic hormone, ADH, that governs the amount of water excreted by the kidney. These osmoreceptors are presumably involved in the drinking behavior induced by a water deficit.

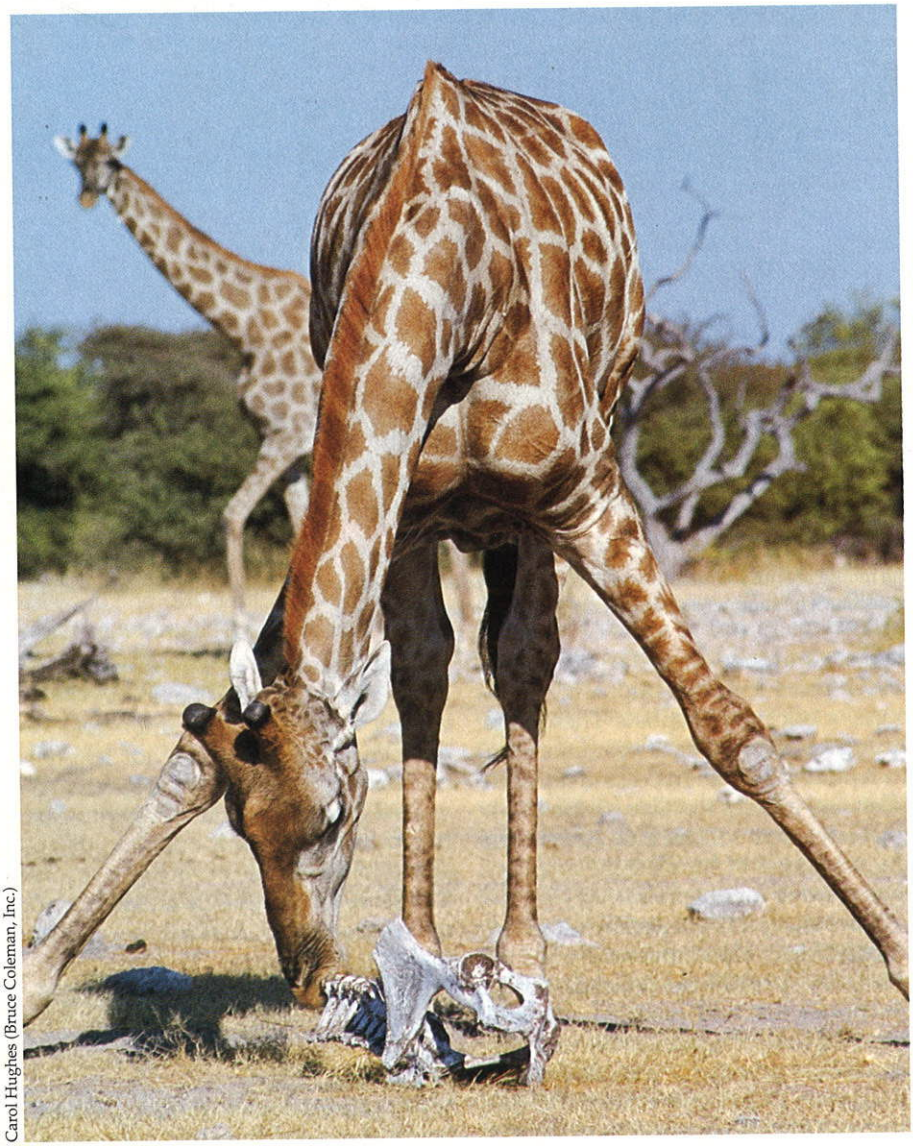
The Swedish physiologist Bengt Andersson has studied osmoreceptors located in the hypothalamus, a structure just in front of the midbrain. He injected minute amounts of concentrated sodium-chloride solutions in appropriate places in the hypothalamus of goats; this caused normally hydrated animals to drink copiously and ingest an amount of water equal to more than one-third of their body weight.

In our studies of camels, my colleagues and I found that a dehydrated camel can drink more than 30 percent of its body weight in 10 minutes, thereby restoring its body-water content to the normal. We observed, however, that the drinking stopped long before water was absorbed from the digestive tract and blood concentrations had declined to a level where the cerebral receptors would stop eliciting drinking. The osmoreceptors are not the only mechanism controlling drinking; other mechanisms are involved in inhibiting further drinking when the correct amount of water has been ingested, although not yet absorbed into the bloodstream.

In our studies of marine birds, we reached similar conclusions about the existence of osmoreceptors. Many marine birds ingest food with a high salt content, and they obviously have no access to fresh water to drink. They manage to excrete an excess of salt, which their kidneys are unable to handle, with the aid of a pair of salt-secreting glands, which in most marine birds are located on top of the skull.

The salt glands are connected to the nasal cavity through ducts and secrete a highly concentrated solution of sodium chloride, which drips off the tip of the beak. We found that a salt load, whether ingested or infused intravenously, induces secretion from the salt glands. Since secretion is elicited also by other osmotic loads, such as hypertonic sucrose solutions, we concluded that osmoreceptors are involved in stimulating salt secretion.

In both birds and mammals, a number of additional endocrine and nervous mechanisms share in the regulatory mechanisms that return internal concentrations to normal levels. We know in considerable detail what these many regulatory mechanisms are, but we do not fully understand why a specific level is required and why a deviation from this "normal" level is opposed. How is this level set, what mechanism is involved in setting the level and why is it essential to defend this level against deviations?



Carol Hughes (Bruce Coleman, Inc.)

Figure 3. Giraffes, when they are low in phosphate, chew on bones. Because bones are composed of calcium phosphate, the phosphate is ingested when an animal chews on them. Bone chewing, or osteophagia, has been observed in phosphate-deficient cattle and reindeer as well.

Regulating Body Temperature

Consider the so-called warm-blooded vertebrates, mammals and birds, which

for the most part maintain a fairly constant body temperature. The normal temperature of humans is about 37 degrees Celsius; deviations from this normal are resisted, and major deviations are harmful. But we do not know why this particular level is desired and aggressively defended. Why is it crucial to maintain precisely this temperature?

The importance of this question and the difficulty in providing a reasonable answer are evident when we consider the body temperature of other higher vertebrates. Consider the normal body temperature of the various orders of mammals. Most eutherian mammals, including humans, maintain a normal body temperature of about 37 degrees Celsius, a level that undergoes regular diurnal fluctuations of about two degrees. If the body temperature increases to somewhere in the vicinity of 43 degrees Celsius, the animal dies—that is, the lethal body temperature is about six degrees above the normally maintained level.

Marsupial mammals likewise maintain a regular and reasonably constant body temperature, but at a lower level than the eutherian mammals, around 35 degrees Celsius. Their lethal temperature is somewhat lower than for eutherian mammals, around 41 degrees, again about six degrees above their normal temperature.

Monotreme mammals, the egg-laying echidna and platypus, maintain a substantially lower normal body temperature of about 31 degrees Celsius. It has been said that because the echidna is a very primitive mammal, it is halfway to being cold-blooded and unable to regulate its body temperature well. In fact, we found in my laboratory that the echidna is an excellent temperature regulator and can maintain its body temperature over a wide range of ambient temperatures, even down to freezing. However, it has a poor tolerance for high temperatures. Its lethal body temperature is again about six degrees above its normal temperature, around 37 degrees Celsius. It is indeed remarkable that the lethal temperature for one group of mammals happens to be the normal body temperature for another group of mammals.

This situation raise two questions. First, why is a temperature that is normal for one group of mammals, the eutherians, lethal to another group, the monotremes? To this question, we have no reasonable answer.

A. Morris (Vireo)

Figure 4. Marine birds have well-developed salt glands that remove excess sodium. Most marine birds eat organisms that are high in sodium. The salt glands, located at the top of the skull, produce a concentrated solution of sodium chloride, which is excreted when the bird's body content of sodium is too high.

The second question is, why are there distinct differences in the normal body temperature among the different orders of mammals? The presumably highest group, the eutherian mammals, have the highest normal temperature. Is a higher temperature better? If so, the monotremes, which have been around longer than eutherians and presumably have had ample time to evolve toward a higher body temperature, should have a higher body temperature. And why haven't all mammals evolved toward body temperatures as high as those in birds, which have normal temperatures somewhere around 40 degrees Celsius?

The answer is that we do not have any answer; we only know that these levels of body temperature are maintained conservatively, as if regulated by thermostats with fixed set points.

Is Fever Beneficial?

Is it appropriate to use the term "fixed set points?" The term "fixed" certainly is not well chosen if we consider the regular diurnal variations in body temperature of a couple of degrees. And what about fever, where the set point can be increased by several degrees and vigorously defended at that characteristic new level?

Fever is recognized as a sign of disease, and the higher the fever, the sicker we are. In a very high fever we might die. Obviously, fever can be bad. A common remedy is aspirin, but does it merely make us feel better, or is a lowering of the temperature really helpful?

The question is: Is it the increased temperature of fever that makes us "sick?" Or is fever a resetting of the thermostat that is helpful in the defense against disease?

If the first suggestion is correct and the high temperature is bad for us, we ought to reduce the fever, as we often do with the aid of an antipyretic agent such as aspirin. We may feel better, but do we really do ourselves any good, or