BRIC 6.10  BU Will Evolve Under Environmental Pressures

_In nature, there is a functional purpose and reason for the shape and color of every living thing._

_- Lee Harrisburger_

Genes will be expressed only if the environmental conditions are favorable. Thus, the presence of a gene, or set of genes, will not completely determine the appearance or behavior of the BU. If the environment is favorable, then the particular behavior or appearance coded by that gene will be manifested. Without the gene, however, the same environment will not likely lead to the same kind of behavior or appearance. The exception would be due to redundant genetic control.

Genes will survive best if they adapt, or allow adaptation. Thus, we would expect that in the presence of a variable environment the BU that survive best are those that are more adaptable. If the environment is relatively stable, then this adaptability is not necessary.

Various environmental conditions that are sure to induce evolutionary changes are the same ones that induce individual adaptations on a short time scale: things such as temperature, availability of food and water, light, and competition. The difference is that those BU that adapt best to new environments are also those that are expected to be more successful at reproduction. Over the course of many generations, the genes from those BU that demonstrate better harmony with their environments will predominate.

For evolution to occur, there must be:

1. pre-existing genetic variation or some means for genetic changes (mutations) to occur
2. an environmental condition that remains over the course of many generations
3. a differential reproductive advantage of the responses of some genes compared to others.

With no variation, there would be no competition allowing eventual genetic dominance; all genes would be alike and all would be equally as suited (or not) to prevailing environmental conditions. Fortunately, there is genetic variation.

Environmental conditions can interact with individual genes to influence whether or not they become active. In this way, the environment can directly influence the development of a BU. Thus, individual cells differentiate into specialized cells, whole organisms acquire individual traits, and ecological systems include mixes of flora and fauna best suited to exploitation of their environs.

Environmental factors may allow an individual to acquire particular traits, but, unless these are able to change the genetic code, they cannot be passed directly to subsequent generations.
The environmental conditions leading to natural selection of certain genetic variants over others must remain stable for many generations. Genes that give a slight reproductive advantage to but one or two generations will not overpower other genes in that time. Thus, genetic variants that best survive are those that are well suited to long-term environmental conditions and adapt to short-term conditions.

During most of the evolutionary continuum for humans, environmental conditions were much different than they are today. Things like air-conditioning, a safe and reliable food supply, clean water, and crowded cities have existed for only a short epochal time. Humans in particular have changed environmental conditions for themselves and for other BU, and this change was relatively recent, at least for themselves and for other species that reproduce at a slow rate. Because of this, genes such as that causing sickle-cell anemia gave a reproductive advantage by protecting against malaria (the gene causes a deficiency of the enzyme glucose-6-phosphate-dehydrogenase and the red blood cells burst when the malaria parasite uses oxygen in red blood cells (Nesse and Williams, 1994)). The gene persists today despite the fact that malaria can be managed in other ways because the history of malaria control is only recent. Other genes such as the ones for Tay-Sachs disease (protects against tuberculosis), and the DR3 gene that causes childhood-onset diabetes (decreases miscarriage rate) are perpetuated even under recent environmental conditions (Nesse and Williams, 1994).

Genetic diseases are relatively rare, in part because most are caused by recessive genes that cause little trouble except in individuals who inherit two copies (Nesse and Williams, 1994). This is a very rare event because the recessive gene must come from both parents, and, if either of the parents is homozygous recessive, that parent will not likely have the same reproductive success as any parent with the dominant gene (Figure 5.3.5).

The shorter the life span, the faster evolution will occur. Thus, the constant and pervasive survival pressure of antibiotics, discovered by Alexander Fleming in 1929, have produced an environment wherein bacteria have developed immunities. In the Oregon Veterans’ Administration Hospital, the rate of antibiotic resistance of staphylococcus bacteria went from less than 5 percent to over 80 percent in a single year (Nesse and Williams, 1994).

Antibiotics were originally produced as natural defense agents against bacterial infections by molds and fungi, also as a result of natural selection in the presence of the environmental pressure of infection. Why then hadn’t bacteria developed resistance to antibiotics, given that molds and fungi have been around for extremely long periods of time? The answer is probably two-fold: first, there probably was some resistance developed, but because these bacteria also existed where there were no molds and fungi, the environmental selection pressure to pass on resistance genes was very low (remember that genetic mutations of resistant bacteria can cause them to become non-resistant), and, second, no one noticed the resistant bacteria because they did not victimize humans.
Selection pressure has been effective in agriculture, where humans have selected plants and animals over many generations to exhibit more desirable traits. Thus, cultivated tomatoes are much different from wild varieties, Holstein cows give much more milk than their progenitors, dogs have many different characteristics from the wolves they came from (see Trut (1999) for an interesting account of selection of foxes for domesticity), and Red Delicious apples are the predominant variety grown in North America. From the standpoint of the genes involved, each of these cases represents a reproductive success.

It might be expected that natural selection should influence the responses of insects to echo location signals of bats, and that is found to be the case (Fenton and Fullard, 1981). Flying moths receiving weak impulses from a pair of auditory neurons, indicating a distant bat, turn and fly away from the bat. Strong stimulation of the auditory neurons causes the moth to fold its wings and dive to the ground.

Inadvertent ecological selection is today favoring certain traits and species and acts against others. Many ecologists (Levin and Schiewe, 2001) are decrying the modern loss of species due to habitat change; at the same time, other species such as deer, woodchucks, wild rabbits, and dandelions are thriving. Human activities are changing environmental pressures on all Earthly species (and soon perhaps other worlds – see box, Section 6.7). Living organisms are bound to change as a result.

That evolution allows organisms to adapt to their environments is embodied in the Island Rule. Large animals isolated on small islands with limited resources tend to become smaller over time. Contrarily, small animals that face reduced predator threats tend to become larger than relatives living in large territories.

Cooperation and competition lead to some interesting views concerning evolution. Darwinian evolution involves a more or less random genetic mutation that can then survive or not depending on its ability to confer a competitive advantage to the organism carrying it. Ben-Jacob et al (1997) present the hypothesis that mutations in cooperative colonies of similar bacteria are directed toward enhancing the colony, although these same mutations give no particular advantage to any specific bacterium within the colony. In this way, bacterial colonies growing in media with limited food resources develop genetic strategies for increasing their utilization of available resources and for seeking out new resources. Patterns of colony growth appear to be genetically modulated and do not involve movement of established cells. The authors conclude that in this cooperative way evolution changes from a system that depends on luck to one that can be controlled, at least in part.

Kessler and Hill (1997) have shown that unconscious cooperation among freely swimming organisms can produce similar benefits to those observed by Ben-Jacob et al (1997). Although interactions among bacteria are not direct, by some means they form complementary swimming patterns that result in bioconvection and better mixing of nutrients and oxygen.
The biological environment is always changing (Bak and Paczuski, 1997). Groups of organisms form ecological units that interact in many ways, often cooperating for the good of the group. Each set of organisms in this group evolves together, changing from generation to generation. Where one generation for one organism overlaps many generations for another organism, the environment may be said to be unchanging for the one with the shortest generation time. However, even there the adaptations make evolution a cooperative venture. Random single mutations and natural selection can eventually reach a state of adaptation that is locally optimal. Further advances must come from many coordinated mutations.

It appears that gradual evolution is only part of the story of adaptation (Bak and Paczuski, 1997). Also possible are catastrophic events that completely overwhelm genetic adaptation. These events may be controlled by humans (for instance) or uncontrolled. The use of an autoclave on bacterial contaminants is a locally catastrophic event for the microbes that is under the control of humans. A comet striking the Earth and obliterating the dinosaurs is an uncontrolled catastrophe. Gradual evolution works best for unchanging environments and has little direct influence on biotic life in the face of a catastrophe.

### Evolution at Work for an Engineer

Evolutionary principles can be used as a design paradigm. Begin with a set of specifications for performance of the final product and a means to quantify progress toward the specification goal. Next, define the starting point or configuration of the product. Then make random changes in the product while measuring how much closer to the final specification is each permutation. If the change improves the product, keep it. If the change does not, then discard it and try again.

This system can be computerized, and has been used to create hundreds of inventions (Keats, 2006). This system automatically mutates a single detail of the product and distributes product characteristics to two parent products. It then mates the two parents to produce offspring. If one child is closer to the ideal than the others, it alone is retained, and its siblings are eliminated. The process of mutation, distribution, mating, and selection repeats until the product comes close enough to the specifications to be acceptable, or until no further improvement is possible (see Figure).

Much of technology develops in a similar fashion, except, perhaps, the step of deliberately introducing random changes is not explicitly taken. Technology often starts with an idea that is
Example 6.10.1. Selection of Pink Salmon

Predict the effect on a pink salmon population of paying fishermen by weight instead of by the piece.

Solution:

Selling by the piece results in catching fish of all sizes; selling by weight prompts the use of nets that capture only the largest fish. Because all pink salmon return to spawn after their second year, the largest fish are the ones with the fastest growth rates. Size selection by fishers promote the survival of the largest and most vigorous fish.
chances of the smaller fish and thereby favor genes for slower growth. Therefore, the genetic makeup of the pink salmon population will be altered toward that for slow growth rates. The longer this pressure continues, the more effect it will have.

Remark:

This is exactly what happened in Canada when the scheme for payment to fishermen was changed in the late 1940’s. A decline of more than 30 percent in average body weight of spawning pink salmon was found in 30 years.

**Applications and Predictions**

1. Pesticides will not work forever.
2. Animals continually bred and raised in a zoo environment will eventually diverge from what they would have been in the wild. They will become better adapted to close quarters, moderate environment, abundant food, and the presence of people. They will lose the ability to hunt, to adapt to the seasons, and to eat intermittently.
3. Some microbes, plants, and animals will become extinct due to the proliferation of humans; others will flourish.
4. New and improved fruits, vegetables, and ornamental plants will be developed by selective pressure.
5. Acquired skills will not be genetically passed on to your children.
6. Fleas will evolve faster than dogs.
7. Microbes will develop resistance to widely-used disinfectants.
8. BU that can use alternative nutrients will survive better than those that can’t in the face of nutrient shortages.
BRIC 6.11  Crowding of BU Produces Stress

Why do people question?
To question is to doubt.

Why do people doubt?
To doubt is to find the truth.

What is the truth?
That’s a good question.  
- Ted Leaptrott

The biological engineer who designs or adapts space for confinement of organisms must do so with care, because there are important implications in the way this is done. Economic considerations would dictate that the largest possible number of organisms be enclosed in the available space. Yet, there are untoward consequences that can be encountered. Depending on the species, there may be social, reproductive, health, or developmental effects to be accounted for.

6.11.1 Antisocial Behavior

Merely as an observer of natural phenomena, I am fascinated by my own personal appearance…. As a matter of fact, my upper lip is pretty fascinating by itself, in a bizarre sort of way.  
- Robert Benchley

Aggression among animals serves the purpose of survival (Southwick, 1970). Aggression against predators defends against being eaten. Aggression against members of the social class helps to establish the fittest individuals for reproductive success. The more aggressive animals become the dominant class, and the most aggressive is the preeminent individual. This animal has access to the most food and the most sexual partners. Hierarchies established in this way are stable and effective.

When these hierarchies are disturbed, new social orders must be established. When two small groups merge, the disturbance is short-lived and the stress is limited. With crowding, however, the number of individuals involved is large, and the possibility of establishing a new, stable social order diminishes. In this case, emotional distress continues unabated.

Extreme aggression when the animals are not in a crowded environment can lead to contrary results. Male birds vocalize their intentions to mate and protect their territories through their songs (see Section 6.19.2). Extremely aggressive birds sing extremely aggressive songs, as indicated by certain pitches and cadences. The most aggressive birds may be set upon by other males acting in concert to kill, injure, or drive away the super-aggressive males. In this case, the males must be aggressive to a certain extent, but not to a degree that they can’t defend.
Laboratory studies on rats have shown that rats raised under crowded conditions exhibited perverse and antisocial behavior (Booth, 1976). The incidence of aggressive episodes increased markedly, which tended to stress the entire community. Those rats that were the most hardy avoided stress by establishing territories in areas that were easiest to protect. Some of the rats engaged in indiscriminate sexual behavior, while other rats became very passive, avoiding sexual encounters, play activities, and aggression. Still others went berserk and attacked almost all others. Social hyperactivity was common. Maternal care suffered, and a great many offspring did not survive to adulthood. Tolerance for new animals declined markedly.

6.11.2 Crowding in Humans

...engineers, whose job it is to harness nature, are required to take action, while scientists, whose task is to understand nature, are not.

- Lyle Feisel

Research results on human crowding are much less clear, perhaps because of the complex nature of the human social environment. Crowded household and neighborhood conditions have been found to have little, if any, effect on human health (Booth, 1976). However, crowded household conditions were positively related to the incidence and severity of stress ailments in males, but not in females. While some studies have shown that household density inversely affects reproduction rates, others have shown no such results (Booth, 1976). Crowded household conditions seem to have a small adverse effect on the physical and intellectual development of children. Children living in congested households are shorter, less heavy, and are sicker than their uncrowded counterparts. Crowded children are not as advanced in school achievement compared to their age peers, and are more often seen by school authorities. Crowding has more health and physical development effect on males, first born, and children over ten than on females, higher birth order, and younger children. Crowding affects school performance of females more than males.

Crowded household and neighborhood conditions have little or no effect on neighborhood participation patterns. Some withdrawal symptoms have been observed in females affected by crowding. However, the more crowded a city, the less likely it is that people would help others in need (Levine, 2003).

The previous study results were obtained comparing conditions within the city, but did not compare urban against rural living (Booth, 1976). More dramatic differences might have been obtained if the social environments were more varied.

Green space can improve a child’s attention span. Children who move to new homes with lots of room around them have been found to have gains in cognitive function.
6.11.3 Personal Space

Scientific trail blazers are routinely treated roughly....Apparently contempt is viewed as a perfectly normal and appropriate response to anyone who thinks outside the box.

- Richard Greenberg

Crowding in humans is a multidimensional concept incorporating physical, social, and personal variables (Insel and Lindgren, 1978). People

Figure 6.11.1. A standing human occupies a personal space of four stacked cubits (Scheflen and Ashcroft, 1976).
tend to be territorial, and to consider an area around themselves as personal space. This personal space buffer zone was found to be within 0.93 m of the man for violent prisoners or 0.45 m for nonviolent prisoners (Insel and Lindgren, 1978). Personal space is dependent upon culture: Germans expand the space, and Mediterranean peoples contract it (Insel and Lindgren, 1978). When this space is violated, then aggressive behavior ensues. Even outside this space, physiological stress increases and blood catecholamines (biochemicals that sustain the “fight or flight” reaction) also increase.

The human personal space is made up of cubical cubits about 46 cm on a side (at least for British and Americans). When standing, a person is about 4 cubits high (Figure 6.11.1) stacked one on top of the other (Scheflen and Ashcroft, 1976). When sitting in a chair the four cubits include one to the

Figure 6.11.2. A sitting human occupies a personal space of four cubits, but in a bent shape (Scheflen and Ashcroft, 1976).
front (Figure 6.11.2). This is the space that is considered to be violated if another person comes too close. Unless the violator is accepted by the person in the space (as for a lover, for instance), the person owning the space will be uncomfortable, defensive, and try to flee. Particularly aggressive individuals may intentionally violate someone’s personal space in order to dominate that person. Personal superiors (for example, a parent) can be more aggressive dominating another’s personal space (for example, a child) than the other way around.

Even caterpillars are territorial. They scrape their teeth on leaves, and the resulting vibrations deter rivals.

Design of enclosures for animals or humans should account for the potential stress induced by crowding (Aiello and Baum, 1979). There is a need to provide a means for individuals to relieve the stress of close proximity (Figure 6.11.3). Room dimensions should be appropriately sized. Males need more personal space than females, and children need more space than adults. Indoor space requirements are greater than outdoor space requirements, perhaps because of the perception of limited escape routes inside. Spaces must appear to be controllable, defensible, and personal. They should be of light color or well-lit (at least for humans), because such spaces are perceived as less crowded and more friendly.

Figure 6.11.3. Privacy is very important for some people.

**Spaces Occupied by Humans**

Human territoriality is evident in this list of facilities. Their designs need to incorporate personal spaces for the occupants.

- Schools
- Airports
- Churches
- Dormitories
- Prisons and Jails
- Hospitals
- Office Buildings
- Libraries

- Stores
- Homes
- Apartment buildings
- Bars
- Restaurants
- Nurseries
- Parks
- Bathrooms
Spaces designed for human occupancy should support characteristics of the occupants as well as the function of the space. Mental hospitals, for instance, need intimate spaces where patients can be alone if they wish (Sommer, 1969). These patients who are rarely physically isolated inside the institution can often be by themselves in parks or adjacent grounds during the day. Another example is school classrooms designed for learning. Increased distance among students fosters less interaction, and physical position (as at the head of a table) confers status on the child occupying that position (Sommer, 1969). Comfortable interaction may be required during part of the school day but not during others, so the physical seating arrangement must be able to be changed to reflect this difference. The study of these personal interactions is called small group ecology.

### 6.11.4 Sensory Overload

*Try to learn something about everything and everything about something.*

-Thomas H. Huxley

Sensory overload affects some people (Heller, 2002). Some people cut the tags from the inside of their clothes because the pricks or tickles they cause are intolerable. Others may stick a piece of paper over a blinking computer monitor icon. Or, some may run their air conditioners in November to drown out the sound of a car alarm on the street that never seems to stop. Add the sound of a dripping faucet, or nails on a chalkboard, or whispers in the next office cubicle. Each of these may overwhelm the tolerance of an individual and cause them to be either deeply disturbed or defensive in their actions.

Premature infants are very sensitive to light, sound, and touch before their nervous systems mature. When overstimulated by any of these senses, the infants may stop breathing and turn blue due to lack of oxygen.

Environmental noise can have both physical and developmental effects on both humans and animals (Cohen et al, 1981). Research has indicated three effects of high intensity noise. First is a narrowing of focus of attention to decrease the amount of information to be processed. This may enhance the performance of simple tasks but be detrimental for complex tasks. Second is a feeling of loss of control over the environment. This leads to depressed mood and lowered initiative. Third is physical arousal leading to long-term increased blood pressure and hormonal excretion. For every 10 dB increase in noise, systolic (heart contraction) blood pressure has been found to increase by an average of 10 mm Hg. Diastolic blood pressure (during heart relaxation) increased 13 mm Hg for each 10 dB increase in noise. Chronic exposure to noise, especially intermittent loud noises, can interfere with learning, behavioral responses, and physical health.
Experts suspect that animals they are trying to breed can also be distracted by external stimuli such as sound or sight. Serious attempts at reproducing these species often require isolation in comforting surroundings. Design of housing, working, health care, and growing facilities should take into account the sensitivities of the individuals resident there.

6.11.5 Animal Spaces

He has done like Orbaneja, the painter of Ubeda;...when he had scrawled out a misshapen cock, was forced to write underneath in Gothic letters, “This is a cock”. -Miguel de Cervantes

Modern farming methods can easily disrupt animal social behavior (Mench and vanTienhoven, 1986). Overcrowding is common, single sex or uniform age groups prevent normal social contacts, and parent-offspring bonds are either disrupted or prevented altogether. The five basic freedoms proposed for animals raised in a production environment are the freedom to:

1. turn around
2. groom
3. get up
4. lie down
5. stretch limbs freely

When these are violated, physiological stress may result, although this is often difficult to prove.

6.11.6 Crowding and Disease

Your three best doctors are faith, time, and patience. -Chinese proverb

The spread of diseases among crowded BU is easier than among more isolated BU. Pathogens that are passed from one individual to another are less likely to be virulent than pathogens that require a vector or alternate host, under normal conditions. That is because individual-to individual contact cannot happen as readily if the individuals are so sick that they cannot move around.

Crowding of individuals modifies this characteristic. Very virulent pathogens can spread from one individual to another if the second cannot escape the first. Thus, whereas natural selection in the wild would have been biased against extremely virulent forms of disease, confinement of large numbers of individuals would select for the most virulent forms.

Agriculture is tending toward concentrated animal production practices. More than 100,000 chickens are housed in the same building, up to
10,000 hogs are raised together, and feedlots can contain 60,000 or more of cattle. When disease strikes these facilities, it can be devastating. Diseases such as avian influenza, cattle shipping fever, and hoof and mouth disease cause large economic losses and health concerns for humans.

6.11.7 Densities in the Wild

If we can really understand the problem, the answer will come out of it, because the answer is not separate from the problem.

-Jiddu Krishnamurti

In the wild there is a natural population carrying capacity for an area. When food, nesting sites, materials, or other essentials become scarce, reproduction slows or ceases, disease incidence increases, or weakened individuals are caught and eaten by predators. Thus, there seem to be mechanisms for the regulation of stable population sizes. Crowding upsets at least some of these mechanisms.

As animals grow from childhood to maturity, they may migrate from their family units to find their own territories where others of the same species do not live. If there are others in the new region, competition for that space can become fierce. Eventually, the natural density of animals reaches a sustainable value.

For plants, too, there is a population density limit. For many plants in temperate climates, the maximum density is determined by access to light. Overcrowded plants tend to be tall and spindly, with small leaves. These plants have poor chances to survive additional environmental insults such as drought or insects (see Section 7.6.3).

Plants cannot move once they are established. As they age, they increase greatly in size. They begin life as small seedlings, and may grow to become trees as large as the Sequoia gigantea. For these organisms, a process of self-thinning occurs as they grow. The more robust individuals grow faster than the less robust, and crowd them out. The less fit individuals die.

In desert areas, water is often the limiting resource, and the greater distance between plants results from water non-availability. Attempting to grow desert plants at greater densities than this will result in the death of many of them.

Microbes and body cells, too, have populations limited to certain numbers depending on nutrient or space availability (see Section 7.6.3). There is active communication among single cells signaling when growth and reproduction is appropriate and when it is not. Under normal circumstances, when the carrying capacity of the environment has been exceeded, the number of cells dying exceeds the number of new cells.
Applications and Predictions

1. Human students wanting to isolate themselves at a table will gravitate toward a position at the end of the table near a wall. Students wanting to discourage others from using the table will sit in the center of the table near an aisle.

2. Humans wanting privacy will face away from the door; humans wanting to defend the room will face the door.

3. There will be a smaller number of elephants than mice in any given area.

4. The density of trees in a forest will decrease as the forest matures.

5. Disease pressure on the occupants of a confined space will be higher than in an open area. Because of this, more drugs and antibiotics will be used. Antibiotic-resistant microbes will be most likely to develop in hospitals.

6. Homes with vaulted ceilings in comparison to a 2.5 m ceiling give a feeling of openness instead of constraint.

7. Crowding affects eating habits.

8. Dorm rooms for males should be designed differently from dorm rooms for females.

9. Merging of social groups permanently disturbs social order.
BRIC 6.12  BU Are Affected by Chemical Stresses

The difference between a deadly poison and a life-saving medicine can be very small; in fact, it is sometimes merely a question of dosage.

- R. E. Schulter

Toxins are present in many forms. There are natural inorganic toxins, natural organic toxins, and, more important in modern life, synthetic toxic compounds.

Toxins usually interfere with metabolic processes. Targets of toxins are enzymes, metallic cofactors (substances that are essential for the catalytic activity of enzymes, binding to the enzyme only during the reaction), and coenzymes (organic cofactor molecules smaller than proteins that bond with the enzyme while the reaction is being catalyzed, and are not altered or consumed by the reaction). Hence toxins are most effective where enzymatic presence is highest in the cell, such as the nucleus, mitochondria, lysosomes, endoplasmic reticulum, and plasma membrane (Reeves, 1981).

Most compounds entering the living organism are subject to metabolic transformations. If they have no nutritive value, they are called xenobiotics (foreign compounds). The metabolism of xenobiotics is intended to reduce their toxicity or facilitate excretion.

6.12.1 Toxicity

Theory guides. Experiment decides. -Anonymous

The following always holds: increased molecular size is associated with increased molecular polarity, which is associated with increased ionization, which increases excretability by the vertebrate kidney, which gives decreased toxicity. Thus, larger molecular size means less toxicity. There are no exceptions to this rule (Reeves, 1981). At least part of the reason that higher molecular mass compounds are generally less toxic than lower molecular mass compounds can be attributed to two traits: 1) greater mass compounds are generally less chemically reactive than lower mass compounds, and 2) greater mass compounds are physically larger and so cannot pass as easily through permeable membranes of capillaries, cells, and organelles. Larger molecules are more likely to carry a net charge and can be more easily filtered by the kidneys.

Many non-polar molecules (e.g. methane and ethane) are biologically inert and require no detoxification. But, if a non-polar molecule is biologically active (e.g. benzene and carbon tetrachloride), it is not easily detoxified (Reeves, 1981).

There are four general classes of biotransformations available to deal with toxic substances:
1. Oxidation. This is a common metabolic response, and involves the addition of oxygen to the molecule or the removal of electrons from an ion. The rate of oxidation is limited, however, so continued ingestion can result in blood accumulation. Alcohol oxidation, for instance, occurs only at 4-8 g/hr.

2. Reduction. This is the change in a molecule by loss of oxygen, addition of hydrogen, or gain of electrons. This is not a common means of detoxification, because the loss of oxygen reduces the molecular mass of the compound (see above).

3. Degradation. Some compounds may require cleavage before further metabolism. The results of degradation are often more toxic than the original compound (see above).

4. Conjugation. Combining the toxin with common substances such as amino acids or carbohydrates makes molecules larger and detoxifies them. This is the most important detoxification mechanism (Reeves, 1981).

Chemotherapy drugs are typically small enough that they can move through the body by means of the bloodstream. Thus, all organs are exposed to these toxic substances. Likewise, once inside tumors their stays are relatively short because they are small and mobile. Macromolecular drug carriers can be linked to chemotherapeutic drugs to reduce their toxicity to nontarget tissues and to lengthen their residence time within tumors. If the macromolecule is soluble then the drug does not have to be mixed with noxious substances to make it more readily carried in the blood.

6.12.2 Dose-Response

The human mind is as driven to understand as the body is driven to survive. -Hugh Gilmore

Toxic effects depend upon dose. Two typical dose-response curves are given in Figure 6.12.1 (Timbrell, 1995). Plotted is the percent response from none (0%) to maximal (100%) against the dose on a log scale. Compound A can be seen to have an immediate effect. There is no dose of compound A that has no effect; consequently, there is no safe dose for compound A.

Compound B has a different-shaped response. There is a range of dosages that result in no response or a response lower than a threshold amount; consequently, there are safe dosages for compound B.

Cellular responses to a mutagen are diagrammed in Figure 6.12.2. There are many possible outcomes, all related to dosage.

One point of extreme interest with any toxin is whether or not there is a safe dose for that toxin. The answer to this question is very important technically and economically, because toxins that have no safe dose must be eliminated completely for perfect safety. A zero-level reference is never
totally achievable because compliance depends on the detection sensitivity of instruments, and that usually continues to increase. Thus, a toxin thought to

![Figure 6.12.1. Two typical dose-response curves. Compound A has no threshold value.](image)

be totally eliminated in the present may be found in the future because monitoring instruments have changed.

To make the issue even more complicated, toxic effects can change depending on the method of administration and on the species used. Most dose-response information about toxins have been obtained from species other than humans, and this always opens the possibility that the other species will not respond exactly as humans respond. If the dose-response data is to be applied to a nonhuman species, then necessary experiments can be conducted to obtain the required information. If the target species is humans, however, then the results will nearly always have some uncertainty associated with them.
Figure 6.12.2. Diagram of responses of a cell to a toxic substance that can cause cancer.
One means to compare the toxicities of different compounds is to compare the dosages that result in death of 50% of those exposed. These dosages are called the LD$_{50}$. Representative LD$_{50}$ information is given in Table 6.12.1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>LD$_{50}$ (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>10,000</td>
</tr>
<tr>
<td>DDT</td>
<td>10</td>
</tr>
<tr>
<td>Nicotine</td>
<td>1</td>
</tr>
<tr>
<td>Tetrodotoxin</td>
<td>0.1</td>
</tr>
<tr>
<td>Dioxin</td>
<td>0.001</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

There are two competing hypotheses relating response to dose (Karam, 2003). The first is the linear, no-threshold (LNT) hypothesis that suggests that all exposure is potentially harmful and that the risk of harmful effects is directly proportional to the dose received. This means that risk of toxic effects can be extrapolated from higher levels down to levels that are vanishingly small (use of the word “risk” here means that measurements are made statistically, and that the only certainty is a probability of occurrence, see Section 4.2.4). The LNT hypothesis has been used to calculate expected cancer rates from extremely small radiation exposures. For example, if the risk from a given radiation exposure is five additional cancer deaths for every 10,000 person-rem, then exposing 10,000 people to 1 rem (a unit of radiation exposure) each should result in an extra five cancer deaths among those people. Using LNT, exposing one million people to 10 millirems each should also lead to five additional cancer deaths. This is like saying that, if a 1000 kg rock will crush someone, throwing a million 1 gram rocks at a million different people will crush someone. Clearly, the calculation may be conservative but not necessarily realistic.

The second hypothesis states that there is a threshold below which no harm accrues, and, further, that lower doses may even be beneficial. When a toxin at high levels is beneficial at low levels, it is called hormesis. Substances exhibiting hormesis are, for example, vitamin D, selenium, aspirin, table salt, water, and, for plants, fertilizer. There may even be a hormesis effect for low-level radiation because this might provide the stimulus for heightened activity of DNA repair mechanisms (Karam, 2003).
6.12.3 High Doses

A chief criterion for the selection of a correct hypothesis...seems to be the criterion of beauty, simplicity, or elegance.

-Murray Gell-Mann

Nutrients can also have toxic effects in large dosages (Figure 6.12.3). The figure shows that at low levels, increasing the amount of nutrients results in increased growth. Then follows a range of nutrient amounts where the nutrient no longer limits growth, and growth does not depend upon amount of supplied nutrient. At very high nutrient levels, there is a deleterious effect that adversely affects growth (Russell, 1961).

![Figure 6.12.3. Nutrients can also be toxic in large amounts (Russell, 1961).](image)

An example of a stimulant that is also a toxicant is the pesticide strychnine. This alkaloid works by neutralizing glycine, an amino acid responsible for transmitting inhibitory nerve impulses to muscles. Without inhibition, the muscles contract but do not relax. Skeletal muscles become hyper-excited and contract continuously. Limbs become stiff and respiration stops. Animals poisoned with strychnine suffocate and die. This poison is toxic to fish, insects, mammals, and birds.

6.12.4 Metabolic Wastes

Carbon dioxide emitted into the air has a 200-year half-life in the carbon cycle.

-Eric Loewen

Metabolic products themselves are often toxic to the BU that produced them. Thus, alcohol is toxic to yeast cells, carbon dioxide is toxic to humans, and ammonia is toxic to birds (see Section 6.4). It is best to remember that metabolic products need to be removed from BU in cultures, bioreactors,
greenhouses, barns, and hospitals in order that the BU not be affected by their own toxic byproducts.

6.12.5 Nanoparticles

*The nanohyperbole meter runs from nanonomic to nanopanacea.*

*George M. Whitesides*

As a general rule, smaller particles may be more toxic than larger ones (Karn and Matthews, 2007). Nanoparticles, those with at least one dimension between 1 and 100 nanometers, can be much smaller than particles of common pollutants, and all are manufactured. Titanium dioxide particles used in sunscreen are about 20 nm in diameter; other nanoparticles are used in electronics, medicine, and coatings.

Nanoparticles have properties not exhibited by larger particles made of the same materials. Bulk gold, for instance, is inert; nanogold catalyses chemical reactions. Some pollutant nanoparticles can penetrate the skin and enter the bloodstream. Carbon nanotubes in the lungs of mice and rats trigger areas of inflammation. Nanoparticles can pass through the nose and into the brain through the blood-brain barrier membrane. Nanoparticles passing into the brains of bass via the gills trigger an enzymatic reaction called oxidative stress. Nanoparticles are too small to settle in water or air, and can be toxic to smaller animals. Aluminum oxide nanoparticles slow plant growth. If bacteria ingest nanoparticles, they could accumulate up the food chain.

6.12.6 Toxins Used As Defenses

*We are engineers, and we should remember two things: first, there are diminishing returns in trying to get past the 90% point instead of just doing the job, and second, we can always work to change the constraints.*

*David J. Dewhurst*

Biological effects of toxins include damage to an organ system, disruption of a biochemical process, or disturbance of an enzyme activity (Schiefer et al, 1997). Many plants and animals purposefully use toxins to protect themselves against predators and competitors. Thousands of chemicals have been isolated from plant tissues, and many of these serve to defend the plants. *Alkaloids* are basic organic compounds containing nitrogen that have poisonous and medicinal properties. Examples include nicotine, quinine, morphine, and cocaine (Hale et al, 1995). *Terpenes* are unsaturated hydrocarbons of plant resins and oils that are toxins and feeding deterrents to many herbivores (Taiz and Zeiger, 1998). *Phenolics* are derivatives of carbolic acid with anti-microbial activity. The phenolic compound lignin is one of the main constituents of plant cell walls (along with cellulose) that cannot be digested by herbivores without help from internal microbes. Lignin
and cellulose may serve, among other things, as a first line of defense against indiscriminate herbivore browsing. Living trees resist beetle attacks by increasing the flow of potentially toxic resin, as well as through other mechanisms of resistance (Birch, 1978).

Each of these classes of compounds is used by plants as protection against predators. Tropical plants seem to contain more toxic alkaloids than do temperate species (Molles, 1999). Despite this, tropical herbivores remove approximately 11% to 48% of leaf biomass in tropical forests, while in temperate forests they remove only about 8%. This higher level of grazing in tropical areas has apparently produced more intense selection pressure for plants with chemical defenses (see Section 6.17.1).

Some animals, as well, use toxins to defend themselves. Some poisonous toads and frogs can synthesize toxins. Others acquire their chemical defenses from plants they eat. The Monarch butterfly is probably the best example of this. The larvae eat milkweed leaves and the toxins are retained in their bodies. The toxins are still there after metamorphosis from larva to butterfly. Birds that eat Monarch butterflies regurgitate their prey and quickly learn to avoid others of the same species.

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**Evolution and Cyanide Tolerance**  
(excerpted from Lane, 2005)

You may have heard about plants with the potential for cyanide toxicity – young sorghum-sudangrass and apple seeds and wild cherry. You may have also heard that very low levels of cyanide are usually not dangerous because animals can detoxify these molecules.

Have you ever considered why animals – livestock and humans – have the ability to detoxify cyanide?

When cyanide is absorbed across the gut wall, the blood carries it to the liver and other cells, where a specialized enzyme system converts cyanide into the non-toxic molecule thiocyanate, which the kidneys then dump into the urine for excretion. But enzyme systems are expensive. It costs energy and nutrients to manufacture all these enzymes, and evolution is notoriously frugal about overspending. So why do animals spend nutritional capital just to build extra metabolic equipment that they would rarely use?

*Because cyanide is actually quite common in the plant world.* Cyanide discourages certain animals like slugs, weevils, and grasshoppers, and plants use cyanide compounds as weapons in their ongoing biochemical warfare to stay alive. The toxic plant species are well-known, but a surprising number of other species can contain low levels of cyanide, including forages like white clover and common vetch and even some human foods like cassava and lima beans.
Toxin Tolerances

A moment’s insight is sometimes worth a life’s experience.
- Oliver Wendell Holmes, Sr.

Tannins (phenolic compounds) in acorns disrupt digestion, and make raw acorns unable to be eaten. Over the years, some groups of people have been able to develop means to deal with this toxin. Prehistoric residents of California mixed unprocessed acorn meal with a certain kind of red clay to make bread. The clay bound enough of the tannin to make the bread palatable. Other groups boiled the acorns to extract the tannin (Nesse and Williams, 1996). This illustrates the point that for every biological measure of defense there is a BU somewhere with a countermeasure. Coping with new environmental chemicals may involve induction of new enzymes or modification of existing ones. Over time there is a gradual elimination of those incapable of adjusting.

It is reasonable to surmise, therefore, that toxins to which BU have been exposed over many generations can be accommodated. It is new environmental toxins that should cause concern.

6.12.7 Toxin Tolerances

Evolution and Cyanide Tolerance cont.

But cyanide is extremely toxic to animals. In animal cells, cyanide irreversibly binds to a critical enzyme called cytochrome oxidase, which controls the last step in the extraction of energy from carbohydrates using oxygen. Cyanide is so devastating because it completely blocks the main energy-producing sequence in a cell. That’s why animals who die of cyanide toxicity have blood that’s bright cherry red – because their cells cannot use the oxygen in the blood, and thus the hemoglobin cannot get rid of it and stays bright red.

Thinking about nutritional evolution, animals like to eat. If animals didn’t have mechanisms for detoxifying cyanide, a lot of animals wouldn’t survive very long. This includes grazers, browsers, and species like omnivorous humans who eat plants as well as animals. Eons of evolution therefore exerted relentless pressure. Genetic lines that developed the equipment for living with low levels of cyanide did a better job of reproducing than genetic lines that lacked this equipment. Maybe not enough equipment to allow us to consume cyanide truffles, but enough to keep us alive when we encounter the occasional molecule.
Embryonic and fetal tissues may be harmed by lower concentrations of toxins than are adult tissues (Nesse and Williams, 1996). As in Figure 6.12.4, toxin vulnerability is greatest around the first trimester of human pregnancy.

To illustrate the extreme specificity of interactions between toxins and their consumers, that sometimes may occur, consider the *Veratrum californicum* plant. If a female sheep consumes this plant on day fourteen of her pregnancy, her lambs may be born with *cyclopia*, having one eye in the middle of the forehead. She can graze this plant before and after day fourteen with no ill effects (Gessert, 2003).

---

Poisonous to Pets

There are some common foods that humans eat that are dangerous to their pets. These include:
- bread dough – may swell and produce alcohol in the stomach of dogs and cats
- onions – cause hemolytic anemia (lysis of red blood cells) in dogs and cats
- grapes and raisins – cause kidney failure of dogs and cats
- avocado – produces cardiac tissue damage, respiratory distress, and mammary gland damage in dogs, horses, rabbits, fish, and birds
- chocolate and cocoa – induces irregular heart beat, irritates the gastrointestinal tract, and triggers epileptic seizures in dogs
- coffee grounds – similar to chocolate

There are a number of common chemicals that can poison your pets. These include:
- flea powder with permethrin (for dogs)
- antifreeze with ethylene glycol (tastes sweet)

And there are many common plants that can be poisonous, too, if eaten. These include:
- Aloe vera
- Daffodil
- Poinsettia
- Tomato leaves
and many others (ASPCA, 2002).
Figure 6.12.4. Vulnerability to toxins in the unborn (Nesse and Williams, 1996).

It has been hypothesized, therefore, that the nausea that accompanies early pregnancy (morning sickness) in humans, cows, and perhaps other mammals is meant to protect the fetus from ingested toxins (Nesse and Williams, 1996). Strong tasting foods often contain toxic substances already touched upon (alkaloids, terpenes, and phenolics) and these are particularly nauseating to newly pregnant women. Because the extra energy demands made by the fetus at this stage in pregnancy are not great, there is little cost to protecting the unborn child by restricting food intake and potential exposure to food-borne toxins.

The same water barrier present on the outside of an organism that lives in the air (see Section 6.1) also can protect against the absorption of toxins from the environment. The integrity of this barrier layer is complex and must be maintained to be effective. The use of soap and water for emergency cleanup of skin exposed to chemicals might actually increase skin absorption in many instances (Cummins, 2004). Solvents are sometimes employed to move certain chemicals past this barrier layer. For example, Dimethyl Sulfone (DMSO) can be used to carry drugs across the skin for dermal administration, or other solvents can be used to administer herbicides to plants.

Solubility differences can lead to some interesting results. People who eat high fat diets have increased lipid levels in their blood. Solvents in the environment can endanger health and often comprise nonpolar liquid and vapor molecules. These are differentially more soluble in lipids than in...
plasma. Thus, it has been reported that people exposed to environmental solvents who also eat high fat diets can carry elevated solvent levels in their blood (Cummins, 2004).

Antibiotics are generally toxic to microbes (although the general term “antibiotic” can be used as well for substances to combat nonmicrobial pathogens and others). Antibiotics are often based upon naturally-occurring substances produced by some BU to combat other BU, and often disrupt microbial cell membranes or metabolism. Microbial immunity to antibiotics can be by the following mechanisms:

1. changes in the cellular membrane that exclude the antibiotic
2. improving efficiency of biochemical mechanisms to pump the drug out of the cell and reduce its concentration below toxic levels
3. development of mechanism to bind the drug or metabolize it into something less toxic
4. changes in enzymatic pathways that either overproduce enzymes that are the target of the drug or change to alternate metabolic enzymes.

### Mysterious Foal Deaths in Kentucky

The spring of 2001 will be remembered for a long time in the horse country of Kentucky. That was the spring that baby horses (foals) died mysterious deaths.

There were precious few clues to the deaths. There were no poisons in the water, nor in the grain eaten by the mothers (mares). The grass was normal, and the air was normal. No unusual pesticides were sprayed to anyone’s knowledge. All anyone really knew was that the $1 billion dollar Kentucky horse industry was reeling.

The answer finally turned out to be a rare coincidence of unusual weather and a cyclical peak in caterpillar reproduction. The population of tent caterpillars reached a 10-year high and they munched on wild cherry leaves to gorge their hunger.

Wild cherry leaves contain substances that can form naturally-occurring cyanide. All livestock owners know about wild black cherry leaves that are safe for animals to eat when they are green and again when they are completely dry. But in the wilted stage they can be deadly.

Unusual weather in March and April increased the potency of young cherry leaves. However, mares rarely had the opportunity to eat
Mysterious Foal Deaths in Kentucky cont.

cherry leaves. Horse owners would have eliminated them from pastures long ago.

This is where the hungry caterpillars came into the picture. They ate the cherry leaves and migrated to other sites, carrying the toxic chemicals with them. Mares ingested the abnormally abundant insect larvae or their feces from grass or water tanks, poisoning their babies in the womb.

This incident emphasizes a broad imperative for humans to understand better the dynamics of nature, and to use that understanding to craft a solution to problems such as this. Mystery solved: now should we spray chemical pesticides, saw down all remaining wild cherry trees, or what?

6.12.8 Toxin Concentration

*Our individual and collective failure to comprehend and act on the connectedness of things is pervasive, systemic, and threatens our health and long-term prosperity.*

- David Orr

As toxins are passed from one trophic level to the next in the food chain they are often concentrated. Many of these materials accumulate in fat tissue and are not detoxified or eliminated from the bodies of those ingesting them. Many more organisms must be eaten than are doing the eating at each trophic level (Figure 6.12.5). Thus, toxins from many BU accumulate in the body of each higher trophic level BU. Eventually, chemicals that were at relatively benign levels at lower trophic stages reach harmful levels at higher stages. Such was the case with DDT, which is a very effective insecticide. Unfortunately, it concentrates to such levels that birds of prey do not deposit enough calcium in the shells of their eggs. When they attempt to incubate their eggs, the eggs break, and drastically lower the birds’ reproductive rates.

Elemental mercury, an inactive by-product of plastic production, was once routinely dumped into rivers and the sea in insoluble form. Bacteria, however, converted the muddy waste into methyl mercury. This very toxic compound has accumulated in the bodies of water-dwelling organisms and in the bodies of humans who have eaten contaminated fish (Table 6.12.2).

The toxins that produce the most difficulty for humans and for other BU are those of the most recent origin. As they concentrate at higher trophic levels they provide selection pressure to accommodate to them, but unfortunately this accommodation includes the loss of individual lives of those who cannot adjust.
Drugs and other biochemicals used by humans do not disappear once used. Whether by excretion or by washing, many more of them end up in waste water than was originally realized. Municipal waste water treatment is designed to deal with solids and microbes, but not most biochemicals. Thus, substances such as antimicrobials, hormones, medicines, and detergents pass through treatment intact and find their ways into the environment either in treated water effluent or municipal solid waste. The water is returned to streams or ground water and the solids are often spread on the land (Brodie, 2007).

Table 6.12.2. Mercury in Seafood Tends to Move Up the Food
<table>
<thead>
<tr>
<th>Species</th>
<th>Mercury Concentration (ppm)*</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Swordfish</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>King mackerel</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shark</td>
<td>0.96</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tuna (fresh or frozen)</td>
<td>0.32</td>
<td></td>
<td>ND**-1.3</td>
</tr>
<tr>
<td>Pollack</td>
<td>0.20</td>
<td></td>
<td>ND-0.78</td>
</tr>
<tr>
<td>Tuna (canned)</td>
<td>0.17</td>
<td></td>
<td>ND-0.75</td>
</tr>
<tr>
<td>Catfish</td>
<td>0.07</td>
<td></td>
<td>ND-0.31</td>
</tr>
<tr>
<td>Salmon (fresh or canned)</td>
<td>ND</td>
<td></td>
<td>ND-0.18</td>
</tr>
<tr>
<td>Shrimp</td>
<td>ND</td>
<td></td>
<td>ND</td>
</tr>
</tbody>
</table>

*parts per million  
**not detectable

What makes this a cause for concern is that these biochemicals can be concentrated in the process of municipal treatment. Many of them are fat soluble, and so can accumulate up the food chain. The presence of antibacterials and microbes in the same mix of waste water could easily lead to the formation of resistant strains of bacteria. There is also concern that people are being exposed to medicines originally taken by others. This problem will only get worse as population growth puts pressure on clean water sources, available land, increased use of drugs, medicines, and disinfectants, and greater reliance on recycling.

6.12.9 Endocrine Disruption

Humans have evolved rapidly as a dominant species because of three characteristics: the desire to know, the ability to question, and both desire and ability to adapt the environment to suit ourselves.

-Evelyn Tiffany-Castiglioni

A chemical that either mimics or blocks the action of natural hormones is called an endocrine disrupter. Most of the known disrupters modify either the production of the female sex hormone estrogen or the abilities of cells to respond to estrogen. Far fewer compounds interfere with the production and function of male sex hormones (androgens, including testosterone). There are naturally occurring phytochemicals that act this way, usually enhancing estrogen production (for example, soybeans produce such products). By far the most troublesome and potent endocrine disrupters are man-made compounds functioning as pesticides, plastics, and industrial chemicals.
Endocrine disruptors are present in much of our environment, and the threats of these compounds seem to be worsening as more and more new biochemicals are being used. Many of these compounds are present in drinking water; it has been found that waste water treatment does not remove many of them, and low concentrations of medicines, pesticides, food preservatives, and industrial chemicals have been discovered in ground water and municipal water.

All of the endocrine disrupting compounds have not been identified, and determining which compounds have this effect is a daunting task. There are nearly 90,000 chemicals that need to be tested, but common chemical structural characteristics have not been found to make the identification easier. To make matters worse, endocrine disruptors may have opposite effects at low and high doses, or may be most potent at low doses (Vandenbergh, 2003).

These compounds can interfere with normal animal development or reproduction. They have been implicated in problems occurring in marine snails, frogs, alligators, and people, among others.

A common estrogen mimic called bisphenol A is found in the lining of food and beverage containers and in dental resins. It leaches into human food and into the surrounding environment. Female mice pups whose mothers were fed bisphenol A during pregnancy were found to have accelerated puberty onset. The effects of this compound were modulated by their fetal exposure to uterine testosterone (Vandenbergh, 2003).

The pesticide DDT is also an endocrine disrupter, and concentrates in predator birds at the highest levels of the food pyramid. DDT causes eggshell thinning and other developmental abnormalities. Eggs in the nest break, and reproduction suffers.

The type of play characterizing juvenile animals varies between males and females, with males generally showing more aggressive physical behavior. Prenatal exposure to testosterone affects this type of play, and litter females situated next to males in the uterus are more likely than females next to other females to engage in male behavior. Contrarily, males with higher estrogen exposure are more likely to behave like females. Endocrine disrupters, especially during pregnancy, can have a large effect on animal behavior throughout their life spans.

Example 6.12.1 Dose-Response Extrapolation

Dose-response curves for toxic chemicals are almost always generated from animals thought to have responses similar to humans. High chemical concentrations are often used because these result in definitive responses in reasonably short times. Predict how these responses can be extrapolated to the low concentrations normally encountered in the human environment.

Solution:

No prediction can be made. Aside from the transfer of response information from an animal to a human, not enough is known about chemical
effects at low concentrations. Some chemicals may continue to be harmful, others may be beneficial at low concentrations. In addition, differences in individual responses will become relatively more important at low concentrations. The result of all these uncertainties is that one cannot say for sure what will happen.

Example 6.12.2 Antimicrobial Plastics

Antimicrobial compounds can be incorporated within plastics that are then molded into useful shapes. Instead of wearing off, as surface applications do with time, part wear just exposes new compound and renews the ability of the plastic to kill microbes on its surface (Alder, 2002). Antimicrobial plastics come in a variety of rod, plate, tube, and thin sheet shapes, and can be used for medical and food applications.

Nonlethal antimicrobial compounds, or those that are less than 100% effective in killing bacteria, would select for microbes resistant to these chemicals. Therefore, it is necessary to select compounds with multiple lethal mechanisms. Metals, especially, and compounds containing metals are good candidates for this application. Silver compounds, for instance, have been used for more than 100 years to control bacteria, mold, mildew, and fungus in medical and food applications. Silver nitrate, for instance, has been used in the eyes of newborn children to protect against disease transmission. Because silver disrupts the cell walls, cell metabolism, and DNA replication, it is not likely that microbial resistance will develop. Thus, incorporating silver compounds in the plastic from which parts are made can be an effective means to combat pathogenic microorganisms.

Example 6.12.3 Why Bt Toxin Isn’t Always Deadly

*Bacillus thuringiensis* (Bt) is a microbe that produces a toxin deadly to several kinds of caterpillars that ingest it. Bt toxin causes mature caterpillar gut cells to swell, burst, and die. Normally, if the Bt concentration is high enough, the caterpillar dies. However, a lower Bt concentration allows surviving cells to emit cytokines (see Section 6.20), which signal gut stem cells to multiply and rapidly form new mature gut cells. If more new cells can be produced than are killed, the caterpillar survives (ASAE, 2001).

Applications and Predictions

1. Many plants will contain toxins in their stems and leaves to protect themselves. These same plants, which depend upon animals to eat their fruits and spread their seeds, will have no toxins in their fruits.
2. Only those parts of the plant that require protection will contain toxins. Thus, the tomato has no toxin in its fruit and the potato has no toxin in its tuber despite the presence of toxins in their leaves.
3. The more toxin produced, the slower plant growth will be.
4. Toxins will be found everywhere.
5. The most conspicuous plants and animals will contain the most toxins.
6. Animals that can defend themselves by aggression, fighting, or flight will not be toxic when eaten.
7. Small biochemical compounds not found in nature will be the most difficult to detoxify.
8. BU will contain more toxins during life stages when they are most vulnerable to predation.
9. Natural toxins can be used to advantage by other BU that acquire them.
10. The same toxin that kills a baby can be tolerated by an adult.
11. Koala bears have special detoxifying bacteria in their gut that enable the bears to eat toxic eucalyptus leaves.
BRIC 6.13 BU Respond to Mechanical Stresses

*Trees are like giant brooms
Sweeping the sky.*

*When they get old and worn
Nothing is left but the handle.*

- Shelia Holloman

BU live in a physical world that challenges them in many ways. There are many stresses incurred from flow of fluids around and through BU, for instance, and the biological engineer must know about these and the consequences of exceeding limits to resisting them. For instance, cells in proximity to a flowing fluid are subject to shearing. As the fluid flows past these cells, friction tends to distort cell shapes by elongating them along the direction of flow. Endothelial cells inside blood vessels grow in such a way that they can better resist shear effects. If shear rate increases too rapidly, the cells cannot adjust, and they may be torn apart. Cells in bioreactors have been known to be destroyed by shear stresses exceeding 20 dynes/cm².

### 6.13.1 Sedimentation and Clotting

*Strength is born in the deep silence of long-suffering hearts, not amid joy.*

-Felicia Hemans

On the other hand, regions of low flow promote deposition or clotting. Sediment and other suspended solids carried along by flowing fluids will be deposited where the fluid stagnates (Johnson, 1999). Thus, a stream that flows rapidly through hilly terrain and picks up a lot of sediment on its rush downhill will drop its load in the lake or marsh into which it flows. High flow rates can suspend a lot of material. Turbulent flow, where there is a lot of mixing and churning, is especially good for moving even very heavy objects. Slowly moving fluids cannot sustain these objects, and they fall. Hence, sedimentation tends to fill lakes, marshes, and river locations where the velocity is particularly low. This not only means that basins will fill with sediment; it also means that benthic plants and animals can be completely covered by unusual sedimentation events. Without access to light, the plants may die and change the ecology of the region.

The clotting system of the blood is not entirely like sedimentation, because it involves biochemical reactions that form clotting compounds (Figure 6.13.1). However, there are similarities, and the one most like sedimentation is that clotting occurs in regions of low blood flow. These are not normally a problem, because *thrombus* (a blood clot) formation is a dynamic process that involves clot formation and dissolution. However, blood that pools in the leg veins during long periods of inactivity can form thrombi. When these break loose from their points of attachment inside the
veins, they can be carried by the blood to other vessels in the body smaller than they are. The result is that the tissue downstream from the occlusion (blockage) receives inadequate oxygen or glucose and dies. Even this may not be life threatening except when that tissue is in the lungs, the heart, or in the brain.

One difficulty with implantation of mechanical hearts, artificial valves, or blood vessels is that there may be regions of blood stagnation inside these artificial organs. Thrombi can form there, and have been known to cause life threatening incidents in organ replacement patients. The difficulty is compounded by the fact that many early biomaterials were sensed as foreign by the body's immune system and it attempted to cover the materials with clot-like depositions.

Figure 6.13.1. Blood clotting occurs when tissue is damaged or when blood stagnates. Reactions cause rod-shaped plasma proteins called fibrinogens to stick together as long, insoluble threads. These adhere to exposed collagen, forming a net that traps blood cells and platelets. The entire mass of fibers and cells is the clot (Starr, 2000).
High flow rates have high amounts of kinetic (moving) energy and low potential (pressure) energy; low flow rates are just the opposite. From an energy balance (see Section 2.2) in the fluid, when a flow stream accelerates its pressure must decrease. It has been observed that atherosclerotic plaque (mostly lipid material) is deposited in blood vessels where the pressure is lowest. Plaque occupies part of the lumen of the vessel and reduces the area through which blood can flow. In order for the same volume of blood to flow through the partially occluded vessel in any given amount of time, its velocity must increase. When that happens, it accelerates and pressure decreases. Reduced pressure is just the condition that caused the plaque formation in the first place, so the situation can easily get worse.

6.13.2 Strengthening and Stiffening

*Man is but a reed, the weakest in nature, but he is a thinking reed.*

- Blaise Pascal

High mechanical stresses require strength. Nothing illustrates this better than trees growing where the wind blows consistently from the same direction. The trees are usually bent to reduce their exposure to the wind, and have gnarled and thickened trunks and branches. Seeing trees growing like this should indicate to the observer that light structures would not survive intact for long in such a place. In fact, estimates of historical wind velocities have been obtained from study of the shapes of trees in the area.

The biological energy necessary to resist wind damage would otherwise be spent on growth and reproduction. Plants that withstand the pressure of wind are often stunted and without many offspring.

Human bone strength has been found to be related directly to intermittent applied forces, similar to (not surprisingly!) forces generated during walking or running. Osteoporosis (weakening of the bones due to resorption of bone material) in the elderly can cause bones to become brittle and break easily. Exercise is one way to reduce the effects of reduced bone density.

The integrity of certain types of bacteria depend on cell walls that they construct. The antibiotic penicillin was effective because it interfered with this construction process (Palumbi, 2001). From the Law of Laplace (Section 2.9.4):

\[
\text{pressure} = \frac{2 (\text{wall tensile stress}) (\text{wall thickness})}{(\text{wall radius})}
\]

(2.9.6)

From this it can be seen that a bacterium can resist higher pressures for thicker walls, smaller size, or walls that are made of stronger materials. Bacteria not round shaped have a radius of infinity, and cannot theoretically resist any pressure, so one reason that bacteria are shaped as spheres and cylinders is that they must be in order not to implode or explode. Cylindrically-shaped
bacteria must have some curvature to the parts of their walls that are straightest, and the walls must be thicker at those parts. The use of stronger materials for their walls is presumably not an option because bacteria utilizing weaker wall materials would have been eliminated from the gene pool long ago.

The Law of Laplace can also be used without the 2 in the numerator for cylinders. The pressure can also be considered the highest pressure that can be resisted from inside out. Thus, we see that smaller blood vessels are stronger than larger ones, all else being equal. But all else is not equal: capillaries must have thin and weak walls to promote diffusion of O₂, CO₂, glucose, and other materials to and from the surrounding tissue. They can have thin and weak walls, and still not burst from internal blood pressure, as long as they are small enough. Which they are.

6.13.3 Critical Shear Stress

*Human genius amazes because it is a mystery. If science could explain how genius came to be, the wonder would be gone.*

-Nathaniel M. Campbell

Individual cells react to mechanical stress in a number of ways. Cells that normally adhere to surfaces and to other cells have more difficulty doing so at high levels of shear stress. Endothelial cells tend to distort and to align their long axes in the direction of the chronic shear. A shear stress of 20 dynes/cm² for 48 hours was found to cause alignment parallel to the flow in aortic endothelium, but caused alignment perpendicular to the flow in the aortic valve. It is not known if the differences in alignment are due to different phenotypes.

Shear stress induces larger amounts of elastin in cells and inhibits tissue calcification. Occludin, a transmembrane protein that forms tight junctions between cells, and is the main contributor to the blood-brain barrier (an obstacle to free passage of complex molecules into the central nervous system), is present in lesser amounts at high shear stress values (about 10% less at 20-30 dynes/cm²).

Shear stress also causes a transient structured disruption of the cell membrane, and increases membrane permeability to Ca²⁺ and other ions (Serbest et al, 2002). It can also increase lipid peroxidation. Shear stresses in the range of 8-14 dynes/cm² begin to damage cells in human vasculature. The percentages of neuronal cells killed *in vitro* varies linearly with the shear stress (Figure 6.13.2) and also linearly with the rate of shear stress application (Serbest et al, 2002).
6.13.4 Stem Cell Substrates

The hardest part (of the research) is that it’s done outside under natural conditions that are changing all the time. -William Manning

Stem cells, those undifferentiated cells that can become almost any type of cell in the body, are apparently affected by the stiffness and the texture of the surfaces upon which they are grown (Figure 6.13.3). Stem cells grown...
on the stiffest matrix become bone cells (Brodie, 2007). The softest surfaces resulted in nerve cells. Stem cells grown on a medium-soft substrate formed muscle cells. Differentiation of stem cells into these types of somatic cells was determined by physical responses instead of the chemical media that they were grown on.

Also, the ability of stem cells to become any type of cell (their pluripotency) is maintained best if they are grown on a surface lined with ridges. The scale of the ridges can vary from nanometers to micrometers without effect (Brodie, 2007).

**Example 6.13.1 Plants Affected by Human Stroking**

A study of plants in Pennsylvania has shown that scientists’ attention can, by itself, alter the way insects feed on plant leaves (ASAE, 2001). A team of ecologists marked 605 plants in 12 plots for study and visited half of the plots weekly. When they visited them, they stroked the plants once each from base to tip to imitate typical contact made when a scientist studies plants in the field.

One species experienced higher insect leaf loss when visited compared to the unvisited control. Several others experienced less leaf loss when visited. Some kinds of plants showed no visitation effects. These results showed that the act of conducting an experiment can, itself, alter experimental results.

As to why this happens, the reasons are open to speculation. Touching a plant may cause changes in its structure or leaf toughness. It may also trigger the release of chemicals attractive to insects. Trampling surrounding vegetation could also alter the target plants’ growth and visibility to insects.
Applications and Predictions

1. Cylinders and spheres will be found to be common biological shapes.
2. Clots will form in regions of stagnant blood flow.
3. If organisms can withstand mechanical stresses, they will have thicker body parts.
4. The larger the surface area, the less pressure can generally be withstood.
5. Anchored plants will not grow in fast-moving streams.
6. The human spinal cord is mechanically strong enough to withstand torsion and compression mechanical stresses.
7. Two strategies are to bend with applied forces or to resist them. Seaweed bends, but a mollusk resists.
8. Paralyzed individuals will need to be exercised to prevent blood stagnation.
9. Guy wires to stabilize a tree need to have sheaths where they contact the tree to better transmit forces to the tree without damage.
10. Clotting is a problem when stents are used.
Optimization is Used to Save Energy and Nutrient Resources

A man who works with his hands is a laborer; a man who works with his hands and his brain is a craftsman; but a man who works with his hands and his brain and his heart is an artist.

-Louis Nizer

Competition in the biological world is usually so great that there is no room for inefficiency. At every turn, in all environments, energy must be conserved where possible because extra energy means better defenses, or better growth, or better ability to garner resources. In all cases, these lead to better reproductive success.

6.14.1 Reproductive Advantage

[Pregnant fruit flies] spent considerable time searching their environment for a suitable spot to lay their eggs. After all, selecting an appropriate site to lay its eggs is presumably the ultimate decision a fly mother has to make, as the consequences of such decisions are likely to have significant impact on the reproductive success of the species.

-Rebecca Yang

Think of the case where there are two BU: one is able to perform the same functions as the second, but it can do so with one half the energy requirements. If each BU is an animal, which is most likely to be caught and eaten by a predator? If each BU is a predator, which is most likely to chase and catch an elusive prey, or which is most likely to survive long times between kills? If each BU is a plant, which is most likely to be able to outgrow competitors and grazing herbivores? If each BU is a microbe, which is most likely to inhabit a region with limited nutrient availability? If each BU is a bodily tissue, which is more likely to confer to the entire organism a reproductive advantage? If each BU is an entire ecosystem, which is most likely to thrive and expand into new territory?

In each of these cases, the answer is clearly that the BU with the energy advantage is the winner of the competition. Only in the instance where competition is at a minimum, say, for example, for the first species in a virgin environment, will there be little primary reason to reduce energy costs. However, as soon as the second species arrives, or even as soon as the number of individuals of the first species increases to the point that they force significant intraspecific competition, there will be an advantage to those individuals that can make more efficient use of resources. Thus, there is a tendency to minimize dependence upon environmental sources of energy and nutrients.

Natural selection is a powerful force leading to evolution of living things (see Sections 5.2 and 6.10). We can, for instance, see evidence of convergent evolution (where organs and tissues with different origins form
identical final forms) and allometric relationships (scaling of different forms and functions among species, see Chapter 7). There is enough competitive pressure in biology that the benefit to cost ratio of almost every biological function must be optimized. A hummingbird, for example, needs enough strength in its wings and energy to be supplied to its wing muscles to hover. There is no advantage to be gained with excess wing strength, and so the benefit to cost ratio changes abruptly after sufficient strength is satisfied. On the other hand, animals that jump have a survival advantage if they can jump farther, faster, or higher. There is an overhead cost of supporting larger muscles or bones needed for better jumping, but the benefit to cost ratio changes gradually for jumping. The biologically-optimal solution for these cases would be expected to be different for each. Thus:

*Each biological form, function, and action has a cost and a benefit. Survival considerations demand that the benefits outweigh the costs.*

### 6.14.2 Locomotion

*Books are the bees which carry the quickening pollen from one to another mind.* – James Russell Lowell

Optimization (see Section 4.4) is a concept that often depends on two resource-consuming processes. One of these increases with some meaningful variable, and one of these decreases with the same variable. Total resource expenditure is given as the sum of these two variables, and, since one increases and the other decreases, there is usually a point where the sum of the two is a minimum.

Take locomotion, for instance. Human walking, which is one form of locomotion, has been found to have a rate of energy expenditure that depends on walking speed (Dean, 1965; Milsum, 1966; Johnson, 1991):

\[
\text{Rate of energy usage} = a + b \text{(walking speed)}^2
\]  

(6.14.1)

Dividing by walking speed gives average power per unit speed:

\[
\text{Average power} = \frac{a}{\text{(speed)}} + b \text{(speed)}
\]

(6.14.2a)

or symbolically

\[
\dot{E}/s = \frac{a}{s} + bs
\]

(6.13.2b)

This represents average power with two components, one linearly increasing with speed and one hyperbolically decreasing (Figure 6.14.1). The average power of walking is a minimum where the sum of the two components is a
minimum, or, the minimum average power can be found by taking the derivative of $\dot{E}/s$ and setting the derivative to zero:

$$\frac{d}{ds}(E/s) = -\frac{a}{s^2} + b = 0$$

(6.14.3)

$$s_{\text{opt}} = \sqrt{a/b}$$

(6.14.4)

where $s_{\text{opt}} = \text{optimum speed, m/sec.}$

Figure 6.14.1. The average power per unit speed for walking has a minimum at a particular speed (Johnson, 2007).

Human walking is energy intensive because it involves the raising and lowering of the body’s center of gravity as the body moves over the extended leg and then as the leg extends backward while the other leg swings forward (Figure 6.14.2). Also, there is a time when both feet are on the ground and
pushing against one another. Eliminating or minimizing the vertical movement of the center of gravity or the time during which the feet are simultaneously exerting forces in opposite directions can increase the efficiency of walking.

Running accomplishes at least some of these goals. During running, only one foot is on the ground at a time. The body does not move vertically as much as it would during walking because each step involves a small leap to the next position. Energy absorbed during the falling stage of each step is stored in the muscles and sinews and recovered during the pushing stage of the next step.

Some animals have other means to reduce the energy inefficiency of locomotion. Animals such as centipedes have so many legs that their bodies do not rise and fall during locomotion. Snakes crawl without the benefit of legs, but their locomotion must overcome the friction created between the ground surface and their skin. Crocodiles use a side-to-side waddling motion to move their legs forward to propel themselves. Fishes’ bodies contain a special swim bladder that allows them to maintain a vertical position in the water without muscular effort. It has been estimated that a 1% improvement in the efficiency of a swimming fish can be expected to make 3% more energy available for growth and reproduction (Alexander, 2003). Birds have wings that convert forward motion into lift to improve efficiency. Humans even use bicycles to propel themselves forward without the rising and falling of the body, and so decrease energy expenditure (Figure 6.14.3).

Walking and running are two possible means of locomotion for humans. Walking is less energy intensive for adult humans than running at speeds of about 2.5 m/sec or less (Johnson, 2007); running uses less energy...
than walking at higher speeds. Walking on the level at 1.3 m/sec requires about 185-370 N·m/sec, whereas running on the level at 4.5 m/sec requires about 223-488 N·m/sec (Johnson, 2007). The transition from walking to running in adult humans appears to be made at the same point at which it is more energy efficient to run than to walk.

![Graph showing power vs. speed for walking, running, and cycling.](image)

Figure 6.14.3. Cycling is more energy efficient than walking or running, despite the extra weight of the bicycle, because the body’s center of gravity stays at a particular level. (Johnson, 2007).

Quadripedal animals also use the gallop as a locomotion means. Galloping involves bending movements of the back that briefly store leg kinetic energy fluctuations as elastic energy, and this contributes to overall efficiency. In addition to the walking-running transitional point, there is also one for the switch from running to galloping.

### 6.14.3 Breathing

*It would be futile to accomplish with a greater number of things what can be accomplished with fewer.* -William of Ockham

Breathing is another organismal process that appears to be optimized. Human breathing at rest consumes approximately 1-2% of total oxygen consumption of the body, whereas during exercise breathing may consume 8-10% or higher. Oxygen consumed by the diaphragm and other muscles...
involved in breathing cannot be used by the skeletal muscles in the legs to escape predators, so it seems apparent that breathing should be accomplished in such a way that exercise oxygen consumption of breathing is minimized. And, indeed, it is.

Breathing at normal frequencies is dominated by resistance (see Section 2.1) located in the airways and lung tissue, and compliance (also see Section 2.1) of the lung tissues. As respiration rate increases, so does the rate of airflow and so does the pressure required to push air through the respiratory resistance. Work rate depends on both pressure and flow rate, so the rate of work required to overcome resistance increases nonlinearly with frequency.

![Figure 6.14.4](image)

Figure 6.14.4. The work of breathing is the sum of two components: that due to resistance and another due to compliance. The sum reaches a minimum at some particular frequency (Johnson, 2007).

The pressure required to store energy in a compliance depends upon the volume stored. At higher respiration rates the lungs are not required to fill as much to deliver the same amount of oxygen to the tissues. Thus,
compliance pressure, and, consequently work rate, is nearly inverse in magnitude to the frequency increase.

The result that we have is work rate composed of two components, one of which increases with frequency and the other of which decreases with frequency (Figure 6.14.4). There is an optimum breathing rate that minimizes work rate, and most published data indicates that people and some other animals breathe at a rate corresponding to the minimum. That is why we breathe faster during exercise: the minimum work rate frequency moves higher as we inhale more air. Not only that, but airway caliber, air flow waveshape, ratio of inhalation time to exhalation time, and lung midposition appear to be adjusted to reduce energy expenditure.

Cardiac parameters related to blood pumping may also be optimized to reduce energy use. Model results appear to be consistent with an optimization hypothesis.

6.14.4 Ecological Optimization

_He who waits to do a great deal of good at once will never do anything._ -Samuel Johnson

Likewise, there is an optimization that occurs within an organism to conserve scarce nutrients. Iron, for instance, is recycled from worn-out red blood cells to be used by new red blood cells. The kidney reabsorbs glucose, bicarbonate, some sodium (depending on intake), potassium, and chloride in order to conserve them and reuse them. Desert animals save water by excreting a very concentrated urine.

Entire ecosystems are also models of efficiency. Populations of species that cohabitate these ecosystems complement and supplement each other. Waste from some species is used as nutrition by others; some plants shade others and cool them, and keep them from drying; large trees protect less hardy species from the wind; nutrients that would ordinarily be lost to the ecosystem are stored in the bodies of organisms and recovered when they die.

While this is not exactly the same as optimization that lends itself to mathematical modeling, it is optimization nevertheless. If a more efficient BU is introduced, it likely has a competitive advantage over existing BU, and the less efficient BU is soon displaced. In this way, biological systems are constantly improving their utilization of scarce resources.

6.14.5 Mode of Action

One idea is that there are two components in the brain – a teacher and a tinkerer. The tinkerer is constantly adjusting things, which produces the background noise; the teacher goes back and fixes or optimizes the changes.

-Sebastian Seung
Of course, the body doesn’t act as a computer dedicated to calculating optimum settings for the muscles and tissues. Optimization and its calculation are mathematical abstractions. Instead, it appears that mechanoreceptors (to measure stretch or force) and chemoreceptors (to measure blood O$_2$ or CO$_2$) are monitored for their outputs (Figure 6.14.5). Small differences in neural signals to the tissues result in small changes in receptor outputs. If the oxygen content of the blood, for instance, decreases, then a different neural signal is sent until the oxygen content increases. And then a larger signal in the same direction can be sent to see if oxygen content rises still farther. If it does, then an even larger signal is sent. If the oxygen content falls, then a smaller signal is sent. By this means, the optimum point can be reached by trial and error, and the optimum point can be tracked as it changes because the neural signal is always being modified by a small amount.

Figure 6.14.5. Trial and error means to find an optimum. This scheme only requires tracking whether receptor outputs are becoming smaller or larger. If the receptor output decreases, then a change is made to increase its output. If the receptor output increases, then a change is made to increase its output. No complicated mathematics is required.
Evidence of the trial-and-error approach is given by variations that occur around the optimal point. It has been already discussed that the walking stride appears to be optimized to reduce the energy expenditure for locomotion. The time for each stride, however, varies by about 6% for adults and 8.5% for children (Chau and Parker, 2004). The frequency of breathing also varies around the optimum value (Figure 6.14.6), thus allowing the optimum breathing frequency to track changes in input conditions such as oxygen consumption.

![Figure 6.14.6. Observed human breathing frequency is not controlled at the exactly optimal value. Rather, frequency varies around the optimal values. Such variation allows better tracking of changes in breathing demand (Johnson, 2007).](image)

**Applications and Predictions**

1. People will learn to perform repetitive muscular motions in the most efficient way possible.
2. Left to themselves, inefficient BU will not survive.
3. To design a new physical process, check first to see if there is a similar process that occurs in nature. Chances are the natural process will use the most efficient means under the circumstances.

4. Desert plants and animals will have developed efficient means to conserve water.

5. Breathing during exercise will be at a faster rate than at rest.

6. Hibernation is a means to conserve resources.

7. The shape of plants is optimized to collect solar energy in the presence of other environmental constraints such as temperature and water availability.

8. Eskimos and polar bears hunt seals in similar fashion because it is most efficiently done that way.
BRIC 6.15 BU Alter Themselves to Protect Against Harsh Environments

*The best way to predict the future is to invent it.*

-Alan Kay

BU are very adaptable, and can tolerate wide ranges of environmental conditions. There are limits, however, and exceeding these results in BU changing forms or states to be able to survive particularly harsh conditions. Of environmental qualities to which the BU must adjust, those of temperature, water availability, and food scarcity are the three that seem to be the most likely to cause major BU accommodations.

These alternative forms and states are of great consequence. Inactive states in animals must be recognized and incorporated into designs if success is to be expected. Inactive forms for bacteria can eventually cause food spoilage or human diseases. Inactive forms for plants are useful means for reproduction. Inactive organs during trauma must be corrected before healing can begin. The biological engineer must then be prepared to deal with these altered states to produce successful endeavors involving BU.

### 6.15.1 Torpor, Hibernation, and Estivation

*Now let us suppose that such a vessel is divided into two portions, A and B, by a division in which there is a small hole, and that a being, who can see individual molecules, opens and closes this hole, so as to allow only the swifter molecules to pass from A to B.... He will thus, without expenditure of work, raise the temperature of B...in contradiction to the second law of thermodynamics.*

-James Clerk Maxwell

Animals change metabolic states in response to temperatures either too high or too low, or the nonavailability of adequate food. Hummingbirds, for instance, have very high metabolic rates (see Section 5.4.4) that must be satisfied by eating roughly 2/3 times their own weights of nectar and insects per day. When hummingbirds arrive at breeding or wintering sites before flowers are abundant, when flowers they visit have decreased nectar production, or when their feeding is reduced by storms, hummingbirds switch to a state called *torpor* (Molles, 1999). In torpor (Figure 6.15.1), metabolism, heart rate, respiration rate, and body temperature are all lowered in order to save energy and allow the animal to survive for relatively short duration environmental extremes (Campbell et al, 1999).

Many small mammals and birds with high metabolic rates exhibit a daily period of torpor adapted to their feeding patterns. This includes most bats and shrews that feed at night and revert to states of torpor during the day (Campbell et al, 1999). Chickadees in cold northern forests may drop their body temperatures as much as 10°C at night. This enables them to survive on energy stored in their tissues.
Figure 6.15.1. When food availability is low, hummingbirds switch to a state of torpor (Molles, 1999).

Torpor appears to be controlled by an internal biological clock. Even if food is made available at all hours to a shrew, it still experiences torpor (Campbell et al, 1999). The need for sleep, and the concomitant slight decrease in body temperature, may be evidence of vestigial torpor in humans.

*Hibernation* is long-term torpor during which the body temperature is lowered in winter when ambient temperatures are low and food is scarce. As the days before winter shorten, some animals will eat huge quantities of food before hibernating. Ground squirrels, for example, more than double their body weight in a month of gorging (Campbell et al, 1999). The body temperature of hibernating ground squirrels may drop to just above freezing, or 2°C (Molles, 1999). Metabolic rates of hibernating marmots (short-legged rodents also called groundhogs or woodchucks) may fall to only 3% of active levels (Molles, 1999). When hibernating, the woodchuck’s heart rate drops from a normal 80 beats per minute to 4 or 5 per minute. Its body temperature falls from 37°C to -3°C, below freezing and the lowest known body temperature of any living mammal.

The altered metabolic state during the summer is called *estivation*. Characterized by slow metabolism and inactivity, estivation allows an animal to survive long periods of high temperatures and scarce water supplies. The metabolic rates of estivating long-neck turtles may fall to 28% of their normal metabolic rates (Molles, 1999).

Both hibernation and estivation appear to be induced by changes in the length of daylight. Artificial lighting can sometimes alter tendencies to hibernation or estivation.
Figure 6.15.2. Tiger beetles seek out environmental temperatures that cause the least stress (Molles, 1999).

Even if they do not react as drastically to extreme environmental temperatures, many insects and animals become inactive during at least part of the day. During cold nights, snakes, lizards, and other small animals hide in burrows where temperatures do not fall as low as outside. Insects such as the predatory tiger beetle hide in the shade (Figure 6.15.2) during the day when surface temperatures on the black sandy beaches of New Zealand, where it lives, reach 70ºC (Molles, 1999).

Animals with reduced metabolism still produce metabolic wastes, although at a rate far lower than they would at higher metabolic rates.
Cellular wastes would build up to poisonous levels (see Sections 6.4 and 6.12) if allowed to accumulate over a long time. Hibernating animals solve this problem by returning to a semi-wakeful state every few weeks, during which time their body temperatures ascend to normal. Their cells flush their wastes, which the animal then excretes. In any engineering design dealing with metabolically-altered states, including artificially-induced hibernation for medical or space travel purposes, provision must be made to allow these wastes to be voided, both at the cellular and at the organismal levels.

### 6.15.2 Endospores

_A competitive world offers two possibilities. You can lose, or, if you want to win, you can change._

-Henry Ford

Actively metabolizing microbes are described as _vegetative_. When essential nutrients are depleted, some prokaryotic microbes form specialized

![Formation of a bacterial endospore](image)

**Figure 6.15.3.** Formation of a bacterial endospore (Tortora et al, 2001).
inactive cells called endospores. These are highly durable dehydrated cells with thick walls and additional layers. They are formed inside vegetative cells by the process of sporulation or sporogenesis (Tortora et al, 2001).

Endospores contain a newly replicated bacterial chromosome and a small portion of cytoplasm inside a double-layered membrane, all enclosed within a thick spore coat of protein (Figure 6.15.3). This coat makes the endospore resistant to many harsh chemicals (Tortora et al, 2001). Most of the water present in the endospore is eliminated, and endospores do not carry out metabolic reactions.

Endospores can remain dormant for thousands of years. This durability and the fact that some very virulent bacteria produce endospores is the reason that they are so dangerous. They are resistant to processes that normally kill vegetative cells.

Germination of the endospore into its vegetative form is triggered by physical or chemical damage to the protein coat. Enclosed enzymes then break down the layers surrounding the endospore. Water enters, and metabolism resumes.

Sporulation is not a reproductive process. One vegetative cell forms one spore, and one spore forms one vegetative cell. There is an extremely small chance that any given spore will return to its vegetative state.

Two genera of bacteria form endospores. The first is the genus Clostridium, an obligate anaerobe. C. tetani causes the disease tetanus; C. botulinum causes botulism; C. perfringens causes gas gangrene and foodborne diarrhea. The second genus is Bacillus, which includes B. anthracis, causing anthrax, B. thuringiensis, a bacterial pathogen, and B. cereus, that can cause a form of food poisoning (Tortora et al, 2001).

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**Anthrax Through the Mail**

Terrorist attacks on the World Trade Center Buildings in New York City on 11 September 2001 were soon followed by letters addressed to the headquarters of a tabloid publisher in Boca Raton, Florida; NBC News in New York City; Microsoft, Inc. in Reno, Nevada; and the Congressional Office Building, Washington, DC. In each of these letters was a little white powder, which testing confirmed contained endospores of B. anthracis.

Because of its easy availability and the durability of its spores, B. anthracis has often been mentioned as a tool for bioterrorists. Anthrax has, at times, been an important disease of livestock in many parts of the world. It wasn’t until 1876 that the German Robert Koch proved that
Processing food to ensure safety requires the reduction of viable endospores to a negligible level. Because it is impossible to ensure that all spores are completely eliminated, a standard reduction rate of $10^{12}$ has been accepted. That means that one surviving endospore for each $10^{12}$ cans

Anthrax Through the Mail cont.

anthrax was caused by a microbe that can change form into one that is extremely inert and hardy (de Kruif, 1926). That was the reason that sheep could contract anthrax in fields that had not seen sheep in many years.

Before 1996, it was appallingly easy to buy anthrax samples from one of the 500 culture collections kept by universities, governments, or private companies. For about $50, anyone could buy anthrax cultures and turn them into bioweapons.

In 1995, however, Aryan Nations member Larry Wayne Harris purchased plague bacteria from the Virginia company American Type Culture Collection and stored the vials in the glove compartment of his car. When he was caught, Congress finally paid attention and passed legislation in 1996 restricting access to deadly microbes including anthrax, Ebola, smallpox, and yellow fever. Since the day of the terrorist attacks on New York City, it is almost impossible to obtain any of these microbes legally (Lemonick, 2001).

When exposed, people can contract the disease in several different forms. Inhaled spores are the most deadly, and need the most powerful antibiotics administered early. The skin form of the disease, from spores that enter the body through small cuts or abrasions in the skin are much less serious and more easy to treat.

Anthrax endospores are only 1-5 µm in diameter. It takes an average of 8000-10,000 inhaled spores to kill an average person (LD$_{50}$), although inhaling only 100 spores may kill some people. Once they have begun to grow, the anthrax bacteria produce a toxin that is the real cause of death.

In the 20$^{th}$ century, 18 Americans have fatally inhaled anthrax spores. The victims include a San Francisco woman who played bongo drums made from infected skins. Others included gardeners who handled fertilizer made with ground bone from infected animals (Park, 2001). Goat and sheep skins from the Mideast are a small but persistent source of anthrax in the U.S. Five more people died of anthrax in the U.S. in 2001 as a result of the anthrax-laden letters they handled.
processed is acceptable. Through a combination of temperature and time, thermal processes for food sterilization can be designed (Johnson, 1999; Teixeira, 1992). Similar considerations are important for sterilization of medical devices and bioreactor growth media.

Endospores are not all bad. Researchers have injected spores of *Clostridium novyi* into animals with cancerous tumors. The spores do not germinate unless the environment is anaerobic, which it is in oxygen-starved tumors. After the spores germinated, the bacteria consumed cancerous cells from the inside of the tumor. Tumors either disappeared or shrank dramatically. The bacteria were engineered to lack their toxin-producing gene, and so were otherwise safe.

6.15.3 Seeds and Spores

*Happiness held is the seed; happiness shared is the flower.*

- Samuel Johnson

Plants also have alternate forms for dealing with harsh environments. These usually take the form of seeds and spores.

To reword an old quip, a plant is a seed’s way of making another seed. Seeds are reproductive forms that each contain an embryo and endosperm tissue to supply nutrients. There is a hard outer protective shell called the seed coat. Gymnosperm plants produce rudimentary seeds from male and female cones, and the plants are called conifers. Angiosperms are flowering plants that also produce grains and fruits. Angiosperms are divided into dicotyledons and monocotyledons depending on the number of seed leaves (or cotyledons) present in the embryo.

Unlike microbial endospores, seeds are not completely metabolically quiescent. Like endospores, however, seeds do not grow unless they are situated in a favorable environment.

During seed maturation the embryo dries and becomes relatively inactive, and remains so during its dormant phase. Seeds may remain viable (able to grow into a mature plant) for many years. Some seeds lose viability after a few years. Others may remain viable for hundreds of years; seeds of *Canna compacta* can live for at least 600 years (Taiz and Zeiger, 1998); *Cassia multijuga* seeds were found to be viable after 160 years, and seeds of *Verbascum blattaria* remained viable for 100 years. Storage conditions will affect seed viability.

In order for a seed to germinate (defined as resumption of embryo growth) water and oxygen must be available and the temperature must be suitable. Optimum temperatures to germinate are different for different seeds. Some seed coats are so tough that germination does not occur until the coat is damaged or removed (Taiz and Zeiger, 1998). In coat-imposed dormancy, the seed coat may prevent water uptake, provide mechanical constraint to growth of the embryo, interfere with oxygen permeability, retain inhibitor chemicals
contained within the seed, or produce inhibitor chemicals (Taiz and Zeiger, 1998).

In other species (i.e., European hazel, European ash, and peach trees), the cotyledons can exert an inhibitory effect on germination growth. If the cotyledons of a peach embryo are removed at an early stage of development, the plant shifts from extremely slow growth and dwarf size to normal growth (Taiz and Zeiger, 1998). It is thought that embryo growth inhibition is due to the presence of abscisic acid (ABA), a growth inhibitor, as well as to gibberellic acid (GA).

Spores are produced by slime molds, by fungi and by vascular plants, the largest group of which are ferns. Spores are smaller and less complex than seeds: many are single reproductive cells that may be as small as 1 µm in diameter (Simpson et al, 1957). Fungal spores may be either sexually or asexually produced, depending on the stability of the environment and the part of the life cycle in which the fungus finds itself. Airborne spores are ubiquitous, and have even been found more than 160 km above the Earth (Campbell et al, 1999).

Spores are reproductive bodies and are usually produced when conditions are favorable for growth. Like seeds, however, spores are able to withstand environmental stress until such time as environmental conditions are favorable for growth.

6.15.4 Storage Structures

*We are survival machines – robot vehicles blindly programmed to preserve the selfish molecules known as genes.*  

-Richard Dawkins

There are other plant structures that are meant to enable the plant to survive through periods of unfavorable conditions. There are bulbs, tubers, and corms that enable a plant to survive cold winters or dry summers by using stored water and nutrients. Storage of body fat and water in animal bodies serves the same purpose. Although these are not alternative forms or states, they are enhanced while the environment is mild to be used when the environment is harsh.

6.15.5 Response to Hemorrhage

*[Competition] requires us to be tough-minded, never hard-hearted.*  

-John Kerry

In another example of a part of an organism that changes its state in the face of brutal environmental conditions, we consider the effects of hemorrhage on the human body. A great loss of blood, even bleeding into internal tissues, can lower cardiac output to the point where blood pressure falls dramatically. In response, the blood vessels constrict to increase resistance (and thus blood pressure), and to reduce blood stored in them. The
veins, in particular, are normally blood storage vessels, and these constrict to move blood back to the heart faster. Contraction of the spleen discharges more blood into the circulation. The heart begins to beat faster. Levels of circulating hormones increase dramatically. Among these are vasopressin, or antidiuretic hormone (ADH), glucocorticoids, aldosterone, erythropoietin, and catecholamines. The first three of these directly affect the kidney, and it essentially stops producing urine (Ganong, 1963; Ruch and Patton, 1966). This altered state of the kidney helps the body cope with the trauma of severe hemorrhage.

**6.15.6 Psychological Trauma**

*There is no exercise better for the heart than reaching down and lifting people up.*  

- John Andrew Holmer

Humans who have experienced some severe psychological traumatic event may even develop an altered psychological state to deal with the event. The sudden death of a loved one, involvement in a serious car accident, or combat experience can produce a traumatic reaction that may include a denial state characterized by sleep disturbances, amnesia, fatigue, and headaches (Smith, 1998). *Post-traumatic stress disorder* (PTSD), also called “shell shock” or “battle fatigue” is common to those who have had to face extreme distress in military or civilian life. PTSD is characterized by negative emotional reactions; in this respect, PTSD is similar to the seed that fell upon rocky ground and did not find conditions suitable for growth (Bible: Matthew 13: 5).

It has been found that high levels of the stress hormone adrenaline is associated with the formation of trauma memory, and that people in whom adrenaline production has been blocked suffer less post-traumatic stress disorder than those who produce the hormone. Thus, quadriplegics (those with the spinal cord severed above the arms) suffer less stress disorder than do paraplegics (those with spinal cords severed above the lower limbs only); the neural connection between the brain and adrenal glands is interrupted for quadriplegics (Lemonick, 2007).

**Applications and Predictions**

1. Endospores are relatively easy to destroy after they have transformed into vegetative cells.
2. Endospores are so small that simple dust masks will not protect against them.
3. The chances of any specific endospore to resprout into vegetative form are extremely small.
4. Seeds may need special treatment in order to germinate.
5. Altered states will make the organism much less destructible, but also much less recognizable.
6. Human blood pressure must be restored quickly in order to enhance chances to survive traumatic injury.
7. It will be difficult to protect against aerial contamination by spores.
8. Buffers in the blood protect against pH change.
9. Starving animals will survive on stored fat and protein.