HONORS BIOLOGY SUMMER ACTIVITIES

Dear _____ ,

Congratulations on entering the Honors Biology Program! To get us started, you will be expected to complete the attached summer assignments by the due dates indicated below and mail to your teacher at:

c/o HPRHS 299 Pidgeon Hill Road, Sussex, NJ 07461
(973) 875-3101

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Teachers:
Ms. Lisabeth Sunda lsunda@hpregional.org
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Ms. Stacey Zaremba szaremba@hpregional.org

Please keep in mind since it is the summer, I might be on vacation too, so be aware that I may not get back to you right away.

The summer assignments are posted online. There are a total of **three** assignments. The **first** assignment is two articles about antibiotic resistance. Please read the articles and answer the attached questions. The **second** assignment is an internet activity "Genetics Science Learning Center". There are **2 parts** to this assignment. Be sure you complete them both by its due date. The **third** assignment is a case study on bottled water. Each assignment should be read entirely and questions should be answered on a separate sheet of paper **(typed)** and handed in by due dates. Assignments may be turned in early, **but no assignment will be accepted late**. Assignments 1 and 3 are worth **25 points** each and assignment 2 is worth **35 points**. These grades will be calculated in your first marking period grade. **DO NOT email assignments**. We have had too many problems in the past with this. All assignments may be mailed to the above address or dropped off and placed in my school mailbox.

The due dates for the three assignments are listed below:

Assignment 1 "Antibiotic Resistance"	DUE Thursday, July 13th
Assignment 2 "DNA Internet Activity" (2 parts)	DUE Thursday, July 27th
Assignment 3 "Ecological Case Study"	DUE Thursday, August 10th

The goal of these summer assignments is to be become familiar with scientific studies that are currently taking place as well as to increase your science literacy. The three assignments are all topics of discussion that will take place during the course of the year.

If you have any problems with assignments, please do not hesitate to e-mail me. Again, I may be away, so leave yourself enough time to read assignments before they are due. Look at your vacation dates too. Make sure your assignment is **postmarked by the due date** to receive credit. Again, **no assignment will be accepted late**. I am looking forward to meeting you in September. Enjoy your summer!

Sincerely,
Ms. Lisabeth Sunda
Mrs. Rebecca Sarno
Ms. Stacey Zaremba

Assignment 1

Antibiotic Resistance

Directions: Read the article "Battle of the Bugs; Fighting Antibiotic Resistance" by Linda Bren and answer the following questions in complete sentences.

1. Why are staph infections such a hot topic in the news today? What type of infections do they cause?
2. How does resistance to antibiotics occur? Explain.
3. In references to viruses, what is another reason why antibiotics are losing their effectiveness?
4. What are three reasons doctors overprescribe antibiotics?
5. What can people do to help reduce antibiotic resistance?
6. How are antibiotics used in agriculture?

Read the article "Antibiotic Resistance" by Carlos F. Amabile-Cuevas and others and answer the following questions in complete sentences.

1. Where do we find the most resistance bacteria and how does it most likely spread?
2. What are some nosocomial infections and research and describe one in a few sentences.
3. Who discovered penicillin and who discovered streptomycin?
4. Explain how antibiotics work. Why are they sometimes referred to as a "magic bullet"?
5. What are some strategies bacteria have developed to defend against antibiotics?
6. What is a plasmid and why are they so dangerous?
7. What are mar genes and how do they work?
8. What is a biofilm and what are the advantages to bacteria living in biofilms?
9. Scientists are currently working on developing new antibiotics. What are some of the sources they have isolated potential antibiotics?

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Battle of the Bugs: Fighting Antibiotic Resistance

By Linda Bren

Ever since antibiotics became widely available about 50 years ago, they have been hailed as miracle drugs--magic bullets able to destroy disease-causing bacteria.

But with each passing decade, bacteria that resist not only single, but multiple, antibiotics--making some diseases particularly hard to control--have become increasingly widespread. In fact, according to the Centers for Disease Control and Prevention (CDC), virtually all significant bacterial infections in the world are becoming resistant to the antibiotic treatment of choice.

For some of us, bacterial resistance could mean more visits to the doctor, a lengthier illness, and possibly more toxic drugs. For others, it could mean death. The CDC estimates that each year, nearly 2 million people in the United States acquire an infection while in a hospital, resulting in 90,000 deaths. More than 70 percent of the bacteria that cause these infections are resistant to at least one of the antibiotics commonly used to treat them.

Antibiotic resistance, also known as antimicrobial resistance, is not a new phenomenon. Just a few years after the first antibiotic, penicillin, became widely used in the late 1940s, penicillin-resistant infections emerged that were caused by the bacterium *Staphylococcus aureus* (*S. aureus*). These "staph" infections range from urinary tract infections to bacterial pneumonia. Methicillin, one of the strongest in the arsenal of drugs to treat staph infections, is no longer effective against some strains of *S. aureus*. Vancomycin, which is the most lethal drug against these resistant pathogens, may be in danger of losing its effectiveness.

Although resistant bacteria have been around a long time, the scenario today is different from even just 10 years ago, says Stuart Levy, M.D., president of the Alliance for the Prudent Use of Antibiotics. "The number of bacteria resistant to many different antibiotics has increased, in many cases, tenfold or more. Even new drugs that have been approved are confronting resistance, fortunately in small amounts, but we have to be careful how they're used. If used for extended periods of time, they too risk becoming ineffective early on."

How Resistance Occurs

Bacteria, which are organisms so small that they are not visible to the naked eye, live all around us--in drinking water, food, soil, plants, animals, and in humans. Most bacteria do not harm us, and some are even useful because they can help us digest food. But many bacteria are capable of causing severe infections.

The ability of antibiotics to stop an infection depends on killing or halting the growth of harmful bacteria. But some bacteria resist the effects of drugs and multiply and spread.

Some bacteria have developed resistance to antibiotics naturally, long before the development of commercial antibiotics. After testing bacteria found in an arctic glacier and estimated to be over 2,000 years old, scientists found several of them to be resistant against some antibiotics, most likely indicating naturally occurring resistance.

If they are not naturally resistant, bacteria can become resistant to drugs in a number of ways. They may develop resistance to certain drugs spontaneously through mutation. Mutations are changes that occur in the genetic material, or DNA, of the bacteria. These changes allow the bacteria to fight or inactivate the antibiotic.

Bacteria also can acquire resistant genes through exchanging genes with other bacteria. "Think of it as bacterial sex," says David White, Ph.D., a microbiologist in the Food and Drug Administration's Center for Veterinary Medicine. "It's a simple form of mating that allows bacteria to transfer genetic material." The bacteria reproduce rapidly, allowing resistant traits to quickly spread to future generations of bacteria. "The bacteria don't care what other bacteria they're giving their genes to," says White. This means that resistance can spread from one species of bacteria to other species, enabling them to develop multiple resistance to different classes of antibiotics.

Combating Resistance

In 1999, 10 federal agencies and departments, led by the Department of Health and Human Services, formed a task force to tackle the problem of antimicrobial resistance. Co-chaired by the CDC, the FDA, and the National Institutes of Health, the task force developed a plan of action. The success of this plan--issued in 2001 and known as the Public Health Action Plan to Combat Antimicrobial Resistance--will depend on the cooperation of many entities, such as state and local health agencies, universities, professional societies, pharmaceutical companies, health-care professionals, agricultural producers, and the public.

All of these groups must work together if the antibiotic resistance problem is to be remedied, says Mark Goldberger, M.D., director of the FDA's office responsible for reviewing antibiotic drugs. "This is a very serious problem. We need to do two things: facilitate the development of new antimicrobial therapy while at the same time preserve the usefulness of current and new drugs."

Preserving Antibiotics' Usefulness

Two main types of germs--bacteria and viruses--cause most infections , according to the CDC. But while antibiotics can kill bacteria, they do not work against viruses--and it is viruses that cause colds, the flu, and most sore throats. In fact, only 15 percent of sore throats are caused by the bacterium *Streptococcus*, which results in strep throat. In addition, it is viruses that cause most sinus infections, coughs, and bronchitis. And fluid in the middle ear, a common occurrence in children, does not usually warrant treatment with antibiotics unless there are other symptoms. (See *Fluid in the Middle Ear*.)

Nevertheless, "Every year, tens of millions of prescriptions for antibiotics are written to treat viral illnesses for which these antibiotics offer no benefits," says David Bell, M.D., the CDC's antimicrobial resistance coordinator. According to the CDC, antibiotic prescribing in outpatient settings could be reduced by more than 30 percent without adversely affecting patient health.

Reasons cited by doctors for overprescribing antibiotics include diagnostic uncertainty, time pressure on physicians, and patient demand. Physicians are pressured by patients to prescribe antibiotics, says Bell. "People don't want to miss work, or they have a sick child who kept the whole family up all night, and they're willing to try anything that might work." It may be easier for the physician pressed for time to write a prescription for an antibiotic than it is to explain why it might be better not to use one.

But by taking an antibiotic, a person may be doubly harmed, according to Bell. First, it offers no benefit for viral infections, and second, it increases the chance of a drug-resistant infection appearing at a later time.

"Antibiotic resistance is not just a problem for doctors and scientists," says Bell. "Everybody needs to help deal with this. An important way that people can help directly is to understand that common illnesses like colds and the flu do not benefit from antibiotics and to not request them to treat these illnesses."

Following the prescription exactly is also important, says Bell. People should not skip doses or stop taking an antibiotic as soon as they feel better; they should complete the full course of the medication. Otherwise, the drug may not kill all the infectious bacteria, allowing the remaining bacteria to possibly become resistant.

While some antibiotics must be taken for 10 days or more, others are FDA-

approved for a shorter course of treatment. Some can be taken for as few as three days. "I would prefer the short course to the long course," says Levy. "Reservoirs of antibiotic resistance are not being stimulated as much. The shorter the course, theoretically, the less chance you'll have resistance emerging, and it gives susceptible strains a better chance to come back."

Another concern to some health experts is the escalating use of antibacterial soaps, detergents, lotions, and other household items. "There has never been evidence that they have a public health benefit," says Levy. "Good soap and water is sufficient in most cases." Antibacterial products should be reserved for the hospital setting, for sick people coming home from the hospital, and for those with compromised immune systems, says Levy.

To decrease both demand and overprescribing, the FDA and the CDC have launched antibiotic resistance campaigns aimed at health-care professionals and the public. A nationwide ad campaign developed by the FDA's Center for Drug Evaluation and Research emphasizes to health-care professionals the prudent use of antibiotics, and offers them an educational brochure to distribute to patients.

The FDA has also drafted a proposed labeling rule that would require specific language on antibiotic labels to encourage doctors to prescribe them only when truly necessary.

Stimulating Drug Development

The FDA is working to encourage the development of new antibiotics and new classes of antibiotics and other antimicrobials. "We would like to make it attractive for the development of new antibiotics, but we'd like people to use them less and only in the presence of bacterial infection," says Goldberger. This presents a challenge, he says. "Decreased use may result in sales going down, and drug companies may feel there are better places to put their resources."

Through such incentives as exclusivity rights, the FDA hopes to stimulate new antimicrobial drug development. Exclusivity protects a manufacturer's drug from generic drug competition for a specific length of time.

The FDA has a variety of existing regulatory tools to help developers of antimicrobial drugs. One of these is an accelerated approval process for drugs that treat severely debilitating or life-threatening diseases and for drugs that show meaningful benefit over existing prescription drugs to cure a disease.

The FDA is also investigating other approaches for speeding the antimicrobial approval process. One approach is to reduce the size of the clinical trial program.

"We need to streamline the review process without compromising safety and effectiveness," says Goldberger. "One of the things that we are trying to look at now is how we can substitute quality for quantity in clinical studies." It has been difficult to test drugs for resistance in people, says Goldberger. "Although these resistant organisms are a problem, they are still not so common that it is very easy to accumulate patients."

From Farm to Fork

Although the inappropriate use of antibiotics in people is a major contributor to antibiotic resistance, it is not the only contributor. Another is the use of these drugs in agriculture. Antibiotics are used in agriculture when they are sprayed onto fruit trees and other food plants as a pesticide for disease control. In addition, antibiotics are used to treat and prevent diseases in food-producing animals and to improve their growth rate.

Scientists have found a link between antibiotic use in agriculture and antibiotic resistance in bacteria carried by humans. "There is a small, but very important, subset of resistant infections in humans that are caused by pathogens that animals carry inherently," says Linda Tollefson, D.V.M., M.P.H., deputy director of the FDA's Center for Veterinary Medicine (CVM). "These pathogens don't make the animal sick, but the animals are treated with antimicrobials for other diseases or to promote growth. These bacteria in the animal may then become resistant to the drug and cause resistant foodborne infections in humans who consume products derived from the animals."

The resistant bacteria, which remain on the animal through the slaughtering and packaging process, make their way into home kitchens. The cooking process kills off many of the bacteria, but undercooked meat will still harbor some. In addition, if raw meat, poultry or fish comes in contact with other foods, bacteria can spread to these foods through cross-contamination.

Most people suffer only mild to moderate illness from these bacteria, but each year, thousands get severely ill and even die. People who do get sick may be treated with the same or a similar drug that is used in the animals and, because of the transfer of resistant bacteria, the drug may not be effective.

The human health impact of antibiotic use in food animals has long been debated. A 1999 National Academy of Sciences report concluded that there is "a link between the use of antibiotics in food animals, the development of bacterial resistance to these drugs, and human disease--although the incidence of such disease is very low."

However, a more recent report released by the Alliance for the Prudent Use of Antibiotics and published in the June 2002 issue of *Clinical Infectious Diseases* recommended eliminating the use of antibiotics for growth promotion in food-

producing animals and limiting farm use of drugs that are critically important to humans. "There is a critical need for more timely action to ensure that antibiotics remain effective," says Levy. "Once the resistance in a bacterial population reaches a certain level, reversal becomes extremely difficult."

The Animal Health Institute (AHI), a national trade association representing manufacturers of animal health products, is also concerned about the possibility of antibiotics used in food animals causing resistant bacteria to develop. But stopping the use of antibiotics in animals is not the solution, says Ron Phillips, AHI spokesperson.

"The number one reason that antibiotic use in animals is important is to keep animals healthy; by keeping animals healthy, we increase food safety," says Phillips. "For farmers, it's an important production tool that contributes to the relatively low cost of our food supply."

The AHI recommends several actions to better manage human resistance. "The first thing we need to do is to be able to appropriately measure it so we can manage it," says Phillips. The AHI supports more and better surveillance of both human and animal resistance, and promoting to farmers and veterinarians better practice of "judicious use" principles regarding antibiotics.

"The FDA has done some good work in helping to promote those principles and ought to continue," says Phillips. But he urges the FDA to work even more closely with the livestock production and animal health communities in promoting judicious use principles. In addition, the AHI calls for "good, sound risk assessments that will yield us the kind of information necessary to make good management decisions."

Animal Drug Regulation

To reduce antibiotic resistance in humans caused by the use of antibiotic drugs in animals, the FDA is evaluating the animal drug pre-approval process, increasing surveillance, and expanding research.

CVM regulates drugs used in food-producing animals. One of CVM's major challenges is improving the way the FDA regulates antibiotics in livestock and poultry, says Stephen Sundlof, D.V.M., Ph.D., director of CVM. "Our main goal is to ensure that human antimicrobial therapies are not compromised or lost due to the use of antimicrobial drugs in animals. But we also have another important goal--to provide for the safe use of antimicrobial drugs in food-producing animals, because these drugs are valuable tools in livestock production and they provide one way of making sure that the food supply is safe."

To balance these two goals, CVM has presented suggested approaches for drug regulation in food animals. These approaches are included in CVM's 1998 publication known as the "Framework Document."

Based on feedback from public forums and advisory committee meetings, CVM is drafting guidance for drug sponsors to help them implement the suggested approaches in the Framework Document. A public meeting will follow the publication of this guidance, which is expected this summer, and the FDA will invite comments on any proposed new or amended rules before they are made final. CVM's approaches, designed to discover whether specific drugs might promote antibiotic resistance, include a more rigorous safety assessment for resistance prior to drug approval and categorizing antibiotic drugs based on their importance to human medicine.

"We decided that not all antibiotics are created equal," says Sundlof. "There are some antimicrobial drugs used in human medicine that are drugs of last resort for treating a life-threatening disease." Animal drugs similar to those used to treat a serious or life-threatening human disease that has no other effective alternative treatment would be subject to the strictest criteria for approval for animal use.

CVM's post-drug-approval approaches include monitoring the development of antimicrobial resistance and collecting data on drugs used in food animal production.

Surveillance

Strengthening the approval process for antibiotics in food animals is only one piece of CVM's multi-faceted approach to the resistance problem. Another important element is surveillance.

Researchers have already established a link between antibiotic use in food animals and human disease. But information regarding where antibiotic resistance emerges, the extent of the threat, and the trends of resistance over time was limited before the creation in 1996 of the largest monitoring system for resistance in the United States--the National Antimicrobial Resistance Monitoring System (NARMS).

Through NARMS, scientists monitor both human and animal bacterial resistance to a panel of antimicrobials selected for their importance in human and animal medicine. As part of this joint effort by the CDC, the FDA, and the U.S. Department of Agriculture (USDA), NARMS scientists collect specific intestinal bacteria samples from people with diarrheal illness and test these samples for antimicrobial resistance at the CDC's laboratory in Atlanta. The NARMS program was recently expanded to include samples provided by 28 state and local public

health laboratories across the country. The program continues to expand and adapt by adding new collection sites and different species of bacteria and antimicrobial drugs for evaluation.

Animal specimens for NARMS are collected from federally inspected slaughter and processing facilities as well as from healthy and ill animals on farms. These samples are then tested for antimicrobial resistance at the USDA's lab in Athens, Ga. In 2001, retail meat samples were added to NARMS, and testing began at the CVM's lab in Laurel, Md. Testing of additional retail meat samples, as well as animal feed ingredients, is being conducted in 2002.

Data provided through NARMS can help support new treatment guidelines, determine the effects of drug usage practices and intervention strategies, and shape national policy regarding the use of antimicrobials in animals.

The high volume of international travel and food imports has intensified the risk of infectious agents and resistant pathogens crossing national borders. In a cooperative agreement with scientists in Mexico, the FDA is sharing its experience with NARMS to help establish a similar monitoring system in Mexico. This system will yield information that may one day be part of an international database, allowing comparison of trends among countries, enhanced food safety activities, improved detection of epidemics, and earlier responses to emerging pathogens on an international scale.

Research

Scientists and health professionals are generally in agreement that a way to decrease antibiotic resistance is through more cautious use of antibiotic drugs and through monitoring outbreaks of drug-resistant infections.

But research is also critical to help understand the various mechanisms that pathogens use to evade drugs. Understanding these mechanisms is important for the design of effective new drugs.

The FDA's National Center for Toxicological Research (NCTR) is studying the mechanisms of resistance to antibiotic agents among bacteria from the human gastrointestinal tract, which can cause serious infections.

In addition, the NCTR has studied the amount of antibiotic residues that people consume in food from food-producing animals and the effects of these residues on human intestinal bacteria. This information led to a new approach for assessing the safety of antibiotic drug residues in people, which may be adopted by the FDA to help review drugs for food animals.

For more information on antibiotic resistance, see the FDA's Web site at

www.fda.gov/oc/opacom/hottopics/anti_resist.html, and the CDC's Web site at www.cdc.gov/drugresistance.

Fluid in the Middle Ear

By Linda Bren

Fluid in the middle ear, also called otitis media with effusion, is a common condition in children. Fluid often accumulates in the ear, just like in the nose, when a child has a cold. In the absence of other symptoms, fluid in the middle ear usually doesn't bother children, and it almost always goes away on its own without treatment, says Janice Soreth, M.D., director of the FDA's Division of Anti-Infective Drug Products. "It usually does not need to be treated with antibiotics unless it is accompanied by additional signs or symptoms or it lasts a couple of months."

If your doctor does not prescribe an antibiotic for your child, do not insist on one. Taking an antibiotic when it is not necessary can be harmful. It increases the risk of getting an infection later that antibiotics cannot kill.

Instead, "observe your child," says Soreth. "If symptoms change, call your doctor to seek further help." Symptoms to watch for include fever, irritability, decreased appetite, trouble sleeping, tugging on the ear, or complaints of pain. "If symptoms occur, it doesn't mean the doctor misdiagnosed the condition," says Soreth. "What started out as a viral condition may have morphed into a bacterial infection several days later. If this happens, an antibiotic may be appropriate."

What You Can Do to Help Curb Antibiotic Resistance

• Don't demand an antibiotic when your health-care provider determines one isn't appropriate. Ask about ways to help relieve your symptoms.

• Never take an antibiotic for a viral infection such as a cold, a cough, or the flu.

• Take medicine exactly as your health-care provider prescribes. If he or she prescribes an antibiotic, take it until it is gone, even if you're feeling better.

• Don't take leftover antibiotics or antibiotics prescribed for someone else. These antibiotics may not be appropriate for your current symptoms. Taking the wrong medicine could delay getting correct treatment and allow bacteria to multiply.

Adapted from the Centers for Disease Control and Prevention.

Citation:

You can copy and paste this information into your own documents.

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ANTIBIOTIC RESISTANCE
by Carlos F. Amabile-Cuevas and others

Mechanisms Preventing Antibiotics from Killing Bacteria Are Appearing Much Faster than Ways to Control Resistance

There is a new monster in American books and films. This monster is not a giant lizard or ape, nor is it a body-snatching alien or an undead creature back to claim its legacy. The new monster is a microscopic agent of disease that is stirred out of its exotic--and remote--locale by people who are unwilling to leave well enough alone. The exotic pathogen is transported back to an urban American center where its lethal and unstoppable effects travel swiftly through the population. Thousands of people die before the lone, outcast scientist finds the pathogen's weak spot, produces a cure and banishes the pathogen, at least for the time being, to the safe confines of the annals of medical history.

The plot has its roots in the recent past, where unusual viruses, such as HIV and hantavirus, and deadly bacteria, such as the so-called flesh-eating bacterium, seem to have appeared suddenly and forcefully on the American public health scene. But in fact many of the newest microbial enemies are neither strange nor exotic. Some of the most dangerous recent public health threats are shockingly familiar--diseases such as tuberculosis and typhoid fever, evocative of a former era when infectious bacteria were often deadly killers.

The reason these and other infectious agents are making a comeback is that they are no longer killed by the drugs that for the past 50 years have kept them at bay; they have become resistant to antibiotics. Antibiotic resistance has also made potential killers out of bacteria that formerly were not much of a threat. And some bacteria are resistant to not just one, but to several different antibiotics, making it difficult for clinicians to hit on a drug regime that will fend them off.

This state of affairs results from an involuntary experiment in evolution and natural selection. The indiscriminate, and, in retrospect, reckless use of antibiotics, has selected for increasingly resistant bacteria. Each instance of antibiotic use kills off only susceptible bacteria. Some small population of resistant organisms is left behind, free to multiply and to pass on the resistance genes to other individuals until eventually resistant organisms outnumber antibiotic-sensitive ones. Within just a few decades, medicine has created these new antibiotic- resistant monsters from what used to seem like a manageable nuisance. What's more, mechanisms of resistance can be passed around from one bacterial cell to another, and even between cells of different (or distantly related) bacterial species. Bacteria also achieve some measure of resistance by forming colonies, which must be taken into account by any researchers hoping to revive old antibiotics and discover new ones.

HOME-GROWN MONSTERS

Historically, outbreaks of infectious disease have been associated with the poor sanitation conditions of crowded urban areas. So it is ironic that one of the best incubators for today's growing number of resistant bacteria is not a stagnant pond or an open sewer, or any of the other traditional breeding grounds for microbes. Many of today's resistant bacteria can be found and spread in the hospital. Often, bacterial strains resistant to one or two drugs enter the hospital via the patients and are spread within the hospital on the hands of hospital personnel, through the air and on hospital surfaces. Clinical isolates of Pseudomonas aeruginosa, resistant because their cell walls no longer admit antibiotics, are a frequent cause of nosocomial infections, those acquired within the hospital. Pseudomonas commonly causes respiratory and urinary tract infections.

Because of the concentrated exposure to antibiotics, hospital strains of bacteria "collect" resistance determinants to drugs and disinfectants at a higher rate than strains found outside of the hospital. As a result, hospitals not only contain more resistant bacteria than other milieus, but they contain more multiply resistant strains than other sites. Bacteria such as Klebsiella, Serratia, Proteus and Enterobacter, which formerly yielded to antibiotic treatments, have become an increasing cause of hospital-acquired infection, especially dangerous because they are multiply resistant to antibiotics. Hospitals, however, are not the exclusive sites of resistance outbreaks, which have been observed in the general population for the past 20 or so years.

Among the most important causes of community-acquired infections is the almost-garden-variety bacterium Escherichia coli. This bacterium is found copiously in the human gut, where it aids digestion. Recently, strains of E. coli that are resistant to several different drugs have been found. Multiresistant E. coli is a common cause of failure of antibiotic therapy in outpatient care and a reservoir of antibiotic- resistance genes.

The first well-documented bacterial outbreak involving multiply resistant bacteria was an epidemic of typhoid fever in Mexico in the early 1970s. More than 10,000 confirmed cases were observed during 1972. Jorge Olarte, then at the Mexico Children's Hospital in Mexico City, characterized the strain of the bacterium Salmonella typhi responsible for the outbreak and demonstrated that it carried genes making it resistant to chloramphenicol (the drug of choice for this infection), ampicillin, streptomycin and sulfonamides. Oddly enough, the same resistance pattern had been observed in Central America, but in Shigella dysenteriae--a different bacterial species. Presumably the genes encoding the antibiotic resistances were passed from the Central American Shigella to the Mexican Salmonella strain.

Lately, much attention has been focused on the resurgence of tuberculosis, a disease that had all but disappeared in industrialized nations thanks to the use of antibiotics.

In the past, these drugs were identified through massive drug-screening efforts. However, no new drugs for tuberculosis have emerged since the introduction of rifampin more than 30 years ago. Now, as multi-drug-resistant tuberculosis strains are isolated with increasing frequency, there has been renewed interest in identifying new therapeutic and prophylactic agents.

Drug-resistant tuberculosis is not new. By the late 1940s, only a few years after streptomycin proved to be the first effective anti-tuberculosis drug, resistant strains emerged. Shortly afterwards, clinicians realized that tuberculosis could easily gain resistance to a single drug and often to two. Three drugs, however, seemed invincible.

In keeping with that philosophy, the Centers for Disease Control and the Food and Drug Administration approved a combination drug containing rifampin, isoniazid and pyrazinamide in the treatment of tuberculosis. Recently, however, not even a three-drug regime is sufficient to treat the newly emerged resistant strains. These are impervious to almost every available tuberculosis drug, and their emergence has resurrected the use of isolated tuberculosis wards in

hospitals--a strategy dating back to the days before antibiotics were discovered. This would at least strike at the root of the problem in drug-resistant tuberculosis, which is patients failing to complete the full course of drug therapy.

Frequently patients start feeling well within 2 to 3 months of starting drug treatment, but it can take up to 18 months before all of the tuberculosis-causing microorganisms are killed. In the past, patients were kept in the hospital for the full course of treatment, so compliance was not a problem. But the move toward outpatient treatment and drug self-administration has fueled the rise in multiresistant organisms. Many people who fail to complete an adequate course of drug therapy relapse and require retreatment. Such circumstances create the conditions for the selection of drug-resistant organisms. For example, in New York from 1982 to 1984, although 9.8 percent of Mycobacterium tuberculosis cells isolated from untreated patients were resistant to one or more drugs, 52 percent of isolates from relapsed patients were resistant.

NATURAL-BORN KILLERS

People tend to think of antibiotics as a human invention when in truth they are perfectly natural. Ever since British biologist Alexander Fleming discovered in 1928 the antimicrobial activity of a substance released from the Penicillium fungus (the substance was called, aptly enough, penicillin), people have appreciated that organisms can manufacture powerful antibiotics. Antibiotics are, in fact, manufactured by the very classes of organisms they aim to destroy--bacteria and fungi. Following Fleming's discovery of penicillin, Selman Waksman from Rutgers University isolated streptomycin from the soil bacterium Streptomyces griseus in 1943.

Scientists are not entirely sure why organisms manufacture antibiotics, and the issue is a subject of some debate. It has often been stated that antibiotics are used by microorganisms as weapons against competing species. Such weapons, the theory goes, are especially useful to organisms that are colonizing a new niche. However, this to us seems somewhat inconsistent with certain features of antibiotics. One would expect that an organism in search of a new environment would not have the resources to make complex antibiotics. Therefore, one might expect antibiotics to be simple compounds, easily made from abundant materials. This, however, is not the case. Most antibiotics are complex and require a good deal of energy for their manufacture. Furthermore, antibiotics are produced by organisms in a stationary phase, which would seem incompatible with competition.

We, on the other hand, agree with Julian Davies of the University of British Columbia, who proposes that antibiotics are vestiges of ancient metabolic systems, dating back to some of the very first organisms on earth. Many antibiotics bind to cellular structures. Although today this specific binding inhibits cellular activity, it could have once facilitated the synthesis of biological molecules such as peptides, or it could have stimulated other metabolic pathways. As biochemistry evolved, these binding molecules were likely replaced by enzymes, which proved more efficient metabolic facilitators. Nevertheless the ancient molecules persisted and now function as antibiotics.

Whatever their evolutionary significance, antibiotics have proved to be powerful weapons against other microorganisms. In general, antibiotics prevent the construction of crucial cellular components, prohibiting the target organisms from proliferating.

Some antibiotics, such as the beta-lactams, a class that includes the penicillins, and the cephalosporins, disrupt the construction of bacterial cell walls. Others, such as the tetracyclines, inhibit bacterial protein synthesis, and still others interfere with DNA or RNA synthesis. Antibiotics are medically useful not only because they kill off unwanted microorganisms, but also because they do not have similar effects on human cells, which are sufficiently different from bacterial cells to escape destruction. In that they can be specifically targeted to particular microorganisms, antibiotics have been called a "magic bullet." This specificity also differentiates antibiotics from antiseptics, which are generally toxic to a variety of cells, be they bacterial or human.

By the late 1950s, but particularly during the 1960s, an explosive search for natural and synthetic antibiotics was under way, eventually yielding about 100 new drugs. And as the costs of producing antibiotics dropped, these compounds were being used for just about any possible purpose: From their appropriate use in therapy against infectious diseases, they soon went on to become supplements for animal feed, where they were supposed to be acting as "growth promoters." Thousands of pounds of antibiotics were released into the environment each year, killing off only the sensitive bacteria. The obvious result had been anticipated by Fleming himself: the emergence and dramatic increase in bacteria that were resistant to the effects of antibiotics.

Where does the resistance come from? Antibiotics are so potentially destructive to microorganisms that they threaten to disrupt the metabolism of the very same organisms that make them. As a result, many microbes develop mechanisms to protect themselves from their own antibiotics. It is this act of self- protection that makes organisms resistant to antibiotics. And research has shown that once an organism becomes resistant to certain antibiotics, it can potentially pass on the resistance to other members of its own species and even to different species.

DODGING THE MAGIC BULLET

Antibiotic resistance, then, is rooted in the bacterial defense against its own harmful antimicrobials. The strategies by which microbes dodge the antibacterial bullet are as varied as the mechanisms of antibiotic activity.

In some cases, enzymes are manufactured by the host bacteria that dismantle the antibiotic molecules. For example, some bacteria acquire the ability to produce and secrete enzymes called beta-lactamases, which degrade members of the beta-lactam family of drugs before they even enter the cell. Enzymes can also be manufactured by bacteria to chemically modify antibiotics such as streptomycin, gentamicin and amikacin so they lose their potency. In some cases, the bacteria can employ another strategy. Sometimes the bacteria modify the shape of the antibiotic's molecular target, so the antibiotic no longer recognizes it and is rendered inactive.

Some drugs, such as the tetracyclines, can successfully gain entry to the bacterium, but the resistant strains have acquired molecular pumps that just pump the drugs right out of the bacteria.

Antibiotic resistance is dangerous when any organism becomes impervious to the effects of a drug. But what makes the current state of affairs even more dangerous is that many of the genes conferring resistance are found on plasmids, small circular pieces of DNA that can be easily exchanged between different bacteria of the same species, or even between individuals of different species. In fact, plasmid exchange between bacteria is probably the single most important mechanism for the spread of resistance genes. Resistance to the beta-lactams, which include penicillin, and the aminoglycosides such as streptomycin, gentamicin, amikacin and others is found on plasmids.

The variety of inactivating enzymes encoded on plasmids is incredible. George Miller and his team at the Schering-Plough Research Institute in New Jersey, for example, have isolated many of the 20 genes encoding enzymes that debilitate the aminoglycosides. He has also classified them based on their evolutionary path, discerning the origins and subsequent transfers of these genes among bacteria.

Recently, an additional mechanism allowing the spread of resistance genes has come to light. Some genes can move from one DNA molecule to others within the same cells. It has long been known that certain so-called mobile genetic elements existed in a variety of organisms, including bacteria. But scientists are just starting to appreciate how important these elements are in spreading and maintaining resistance genes within bacterial populations. For example, a single

bacterial cell can contain many different plasmids, and genetic cassettes containing resistance genes can be exchanged between them. In this way a single plasmid may obtain several different resistance genes before it is passed on to another cell. Genetic mobility within bacteria augments opportunities for gene flux among different DNA molecules and between different cells within a microbial population.

Where do resistance genes come from initially? Most of them are identical or very similar to those found in antibiotic- producing organisms. It is possible that these genes traveled from the microbes in which they first arose, to the ones responsible for infections in people and animals. In 1973 Julian Davies and Raoul Benveniste (both then at the University of Wisconsin) first noticed the similar biochemical mechanisms of resistance between the aminoglycoside-producing bacteria and common pathogenic microbes. More recently Davies has found DNA sequences containing antibiotic-resistance genes in commercial antibiotic preparations. This DNA may be taken up by pathogenic bacteria even during the course of antibiotic therapy.

A number of bacterial responses to environmental stress result in the increased resistance of bacteria to antimicrobial drugs. Unlike the previously described mechanisms of resistance, the genes encoding these resistance mechanisms reside not on plasmids, but on the bacteria's main chromosome. Genes that encode multiple antibiotic resistance, called mar genes, described by Stuart Levy of Tufts University, are turned on in the presence of at least two different antibiotics, tetracycline and chloramphenicol, as well as salicyclate, which is the active ingredient of aspirin. The drugs act in this case as an environmental stressor. The presence of these stressors leads to a temporary bacterial resistance to many other drugs.

Many drugs enter a bacterium via molecular pores on the surface of the bacterial target. The mar gene products initiate a series of events that ultimately block the expression of pore genes and thus inhibit pore formation. When this happens, the outer membrane becomes less permeable to drugs, which then cannot reach their targets within the cells. This mechanism confers resistance to several unrelated types of antibiotics--all those that rely on the pores to gain entry to the bacterium. This form of resistance cannot last forever, however, as the membrane becomes less permeable not only to unwanted drugs, but also to much-needed nutrients. Pore inhibition lasts only as long as the bacterium senses the chemical stress, in this case the presence of the antibiotics. When the antibiotics are gone, the pores reform, and the bacterial functions return to normal.

Another regulated system, which overlaps with mar, is the response to superoxide, which are produced by human immune cells to destroy bacteria. The bacterial response to superoxide is governed by the bacterial soxRS genes, described by Bruce Demple at the Harvard School of Public Health. The soxRS genes, like the mar genes, reduce the expression of membrane pores and make the bacteria resistant to both antibiotic drugs and the immune system's superoxide. Bacterial resistance to immunological superoxides renders the bacteria more virulent since the immune system becomes ineffective at disabling it.

The resistance genes involved in both the mar and soxRS systems are found on the main bacterial chromosome. Genes in this category are generally involved in cell regulation. Sometimes genes encoded on plasmids can become irreversibly incorporated into the chromosome, but this is rare. Chromosomal mutations usually reduce the ability of the bacterium to survive in environments free of antibiotics and may also render the bacterium less virulent. Finally, chromosomal resistance genes, unlike resistance genes on plasmids, are unlikely to be transferred between different bacteria.

GROWING TOGETHER

Interactions between bacteria are facilitated by the way bacterial colonies are formed, placing individual bacteria, sometimes of different species, in close proximity. Bacterial colony formation may also help to explain some forms of resistance and should be taken into account by

researchers developing antibiotics.

Antibiotics were and still are developed on the basis of test-tube or in vitro experiments. Clinical tests, or antibiograms, to determine the antibiotic sensitivity of bacteria found at sites of infection, are also carried out on test-tube- grown bacteria. In both cases, bacteria are grown "planktonically," that is, in homogeneous suspensions of liquid medium. This condition may not reflect the way in which bacteria grow naturally when causing an infection and, in particular, may result in a substantially different susceptibility to antibiotics.

Bacteria in aquatic environments, both natural and artificial, and in infected tissues have an extraordinary tendency to interact with surfaces to form associations called biofilms. These cooperative consortia have been studied by J. William Costerton and his group at the Center for Biofilm Engineering in Montana. The bacterial cell produces a variety of complex sugars to form a coat named the glycocalyx, which assists in firmly gluing the cell to inert surfaces. Cell division takes place inside the glycocalyx matrix and results in the formation of microcolonies. Continuous reproduction and the attachment of bacterial cells of different species result in a heterospecific biofilm.

The application of confocal scanning laser microscopy to the study of biofilms revealed an amazing architecture. Highly permeable water channels exist to permit the penetration of large molecules in a primitive "circulatory system" that delivers nutrients from the environment to the microclimate niche and removes the metabolic waste products at the same time. Bacteria within a mature multispecies biofilm live in a special microniche where nutrients are provided by neighboring cells and by diffusion. In this way, microcolonies of cells capable of primary production of nutrients are often surrounded by microorganisms with larger nutrient requirements. The physiology of biofilm cells is very complex and different from that of cells grown planktonically. The physiological status of attached cells can vary depending on the location of each individual cell within the multiple layers in the biofilm.

Bacteria obtain a number of advantages by living in biofilms. Cells are protected from environmental stresses such as heat, ultraviolet radiation and viruses. They are also protected from antibacterial agents. The resistance of biofilms to antibacterials can have serious medical consequences, since biofilms can form on catheters, implants, dental units, silicon surfaces, contact lenses, endotracheal tubes and so on. Antibiotics cannot eliminate these biofilms. The only way to arrest the infection is to replace the affected device.

The structure of biofilms changes the susceptibility of resident bacteria to antibacterial agents. Bacterial cells grow embedded in a thick layer that constitutes a solute phase distinct from the bulk fluid phase of the system. Biofilms generate a sheltered, encapsulated community of cells in which environmental stresses are greatly reduced. Changes in the surrounding medium cause alterations in the susceptibility of bacteria to antibiotics. The resistance of Pseudomonas aeruginosa, for example, to polymyxin B and aminoglycosides increases under conditions of magnesium depletion (a likely situation within a biofilm). In addition, it has been shown that biofilm cells produce 32 times more beta-lactamase enzymes, which destroy the beta-lactam family of antibiotics, than do cells of the same strain grown planktonically.

The formation of biofilms may be the heart of some kinds of antibiotic resistance. It is possible, for example, that the glycocalyx forms an impermeable barrier to antibiotics, so individuals buried within the biofilm are never exposed to the drugs. Living in a biofilm may cause the activation of genes associated with a sedentary existence. Coincidentally, these genes may also affect the susceptibility of the bacteria to drugs.

It is also possible that the limited availability of key nutrients within the biofilm slows down the growth rate. As a result, some of the bacteria, particularly at the base of the biofilm, may be in a dormant state. Some kinds of antibiotics exert their influence only on actively growing cells, so dormant cells would resist those antibiotics.

Planktonic and biofilm cells are known to coexist at sites of infection. When these cells are exposed to antibiotics, planktonic cells and those at the surface of the biofilm are quickly affected. The excess antibiotic molecules that have entered the cells and that are not engaged in cell inactivation are probably destroyed by antibiotic-degrading enzymes or are involved nonspecifically with other cellular components. The rest of the antibiotic molecules are trapped by glycocalyx, which is negatively charged and is known to function as an ion-exchange resin (like those used to purify water and other compounds), capable of binding a very large number of antibiotic molecules.

To overcome resistance brought about by biofilms, new drug strategies are needed. Combinations of antibiotics have been used successfully against some biofilms. For prosthetic devices and biocompatible materials, however, the future is uncertain. For example, the bacteria Proteus and Pseudomonas bind effectively to orthopedic devices coated with gentamicin that were specifically designed to prevent biofilm formation, as shown by Chung-Che Chang and Katharine Merritt at Case Western Reserve University.

FACING RESISTANCE

Taking into account a more realistic model for bacterial growth in biofilms may go a long way toward improving drug development and testing strategies. But of course other approaches must be taken as well. It is important to understand that the outcome of any, or perhaps all, strategies is unpredictable, as science is playing a catch-up game with bacteria that are continually evolving.

In our laboratory, we have been looking for ways either to eliminate resistance-encoding plasmids from their bacterial hosts or to prevent the expression of resistance genes encoded on them. There are several reported chemical agents capable of doing that, but most of them are very toxic. Some agents eliminate plasmids at concentrations that kill the bacteria. If this happens, a resistance mechanism will soon arise because of the strong selective pressure.

So far, the most promising agent has been ascorbic acid, better known as vitamin C, which has effectively eliminated resistance plasmids from Staphyloccoccus aureus. Ascorbic acid may not turn out to be the ultimate drug for plasmid elimination, since very high concentrations are needed to obtain the effect, but it may lead the way to similar, more effective compounds. Another novel approach to eliminating resistance is taken by Jack Heinemann at the Rocky Mountain Laboratories in Montana. He has proposed the possibility of halting the spread of resistance genes by inhibiting gene transfers between bacteria.

From the point of view of the pharmaceutical industry, the simplest way to face the threat of antibiotic resistance is to chemically modify existing drugs. Modified compounds, also called semisynthetic antibiotics, usually have the same or slightly improved pharmacological properties as existing drugs, but are resistant to the inactivating enzymes. Isepamicin, for example, is in the aminoglycoside family of antibiotics, but is insensitive to most of the aminoglycoside-inactivating enzymes found among resistant bacteria. The so-called third-generation cephalosporins include drugs resistant to some beta-lactamases. However, if modifying the drug molecule is relatively easy, it seems just as easy for the bacteria to evolve a new deactivating enzyme in response.

Another possible approach to circumvent resistance is the development of agents that inhibit the resistance mechanisms themselves, restoring bacterial susceptibility to old drugs. Several compounds that inhibit the beta-lactamase enzymes are already in clinical use. Other compounds that diminish tetracycline resistance are currently being studied. Stuart Levy and his colleagues at Tufts are trying to identify molecules that are structurally similar to tetracycline, which can bind to and clog up the molecular pumps that shunt tetracycline out of the cell in resistant bacteria. That way, actual tetracycline molecules can be used again for as long as the pumps remain gummed up.

In addition to rehabilitating old antibiotics, pharmaceutical scientists are trying to develop completely new antibiotics. Some groups are screening numerous potential antibiotic sources and then identifying and isolating the active molecules. Their search has produced squalamine, a steroid isolated from sharks, as well as cryptdin and cecropin, isolated from the mammalian intestine, and ranalexin, which was derived from frog skin.

Investigators are also going back to the original source of antibiotics--microorganisms. They are screening organisms such as soil bacteria to see whether any new and useful antibiotics have appeared. For example, such a search led research teams headed by George Miller at Schering-Plough to find everninomycin, which may serve as the prototype for an entirely new family of antibiotic drugs, for which no resistances have so far been discovered. But the potential for resistance is one possible disadvantage in microbial sources for antibiotics. The organisms producing these antibiotics probably already have resistance mechanisms against the drugs. If the genes encoding these mechanisms are located on plasmids or any other transferable genetic molecule, the resistance can spread to disease-causing bacteria, which would set the cycle in motion again.

Another sophisticated way to direct the search for new antibiotics is rational drug design, which uses information about the structures of molecules to create or modify drugs. Researchers at Hoffmann-La Roche in Switzerland have already rationally designed inhibitors of antibiotic-modifying enzymes.

The search for and development of new drugs by the pharmaceutical industry will go a long way toward conquering the growing microbial resistances to available antibiotics. But there is much more to be done than merely generating new antibiotics-- the pace of which cannot keep up with the microbial resistance responses.

A significant change of attitude must also be encouraged among physicians, industry and the public. Antibiotics must be seen as a valuable resource that should be used carefully and only when really needed. The judicious use of antibiotics and the dangers of bacterial resistance must be taught worldwide in the early years of medical training, and it must continue to be taught to medical practitioners throughout the course of their careers. The efforts undertaken by the Alliance for the Prudent Use of Antibiotics led by Stuart Levy must receive much stronger support. Industries must stop pushing for the nonclinical use of antibiotics, which accounts for most of the sales of several drugs. The pharmaceutical industry must realize that it will benefit from the rational use of antibiotics and should provide financial support for these efforts.

Finally, a worldwide campaign to eliminate over-the-counter preparations of antibiotics, especially in countries where all antibiotics are sold over-the-counter, should be promoted. The spread of antibiotic-resistance genes is not restricted by political geography, and self-administered antibiotics may account for a significant fraction of antibiotic misuse.

The history of antibiotics reminded our student Raul Borbolla of the Greek myth of Sisyphus, the king of Corinth who, as a punishment for his hubris, was condemned by the gods to push a boulder up a mountain, only to have the boulder roll to the bottom, from which Sisyphus had to start pushing again. Again the boulder would roll to the bottom, and the cycle was repeated into perpetuity. The rational and controlled use of antibiotics may prevent medicine from facing Sisyphus's fate.--Carlos F. Amabile- Cuevas, Maura Cardenas-Garcia and Mauricio Ludgar

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* * *

Figure 1. Outbreaks of bacteria resistant to more than one antibiotic have been documented since the early 1960s.

date: 1960-1970
place: USA (St. Paul, Minn.)
microorganism: Neisseria gonorreae
disease manifestation: gonorrhea
resistance: penicillin
number sick: 250,000-500,000

date: 1963-1967
place: USA
microorganism: Salmonella typhi
disease manifestation: diarrhea
resistance: chloramphenicol, streptomycin, tetracycline, sulfonamides
number sick: 3,025 (43 deaths)

date: 1968
place: USA
microorganism: Streptococci
disease manifestation: nosocomial (hospital-acquired) infections usually affecting respiratory and urinary tracts, but not exclusively
resistance: sulfonamides
number sick: 1,020

date: 1969-1970
place: USA
microorganism: Salmonella Klebsiella pneumoniae
disease manifestation: diarrhea
resistance: multiple drugs
number sick: 19

date: 1972-1973
place: Mexico
microorganism: Salmonella typhi
disease manifestation: typhoid fever
resistance: chloramphenicol, streptomycin, tetracycline, sulfonamides
number sick: 10,000-15,000

date: 1976-1979
place: Canada
microorganism: Salmonella typhi
disease manifestation: diarrhea
resistance: multiple drugs, including ampicillin, cephalothin, chloramphenicol kanamycin, nalidixic acid, nitrofurantoin, streptomycin, sulfonamide, tetracycline
number sick: 416

date: 1977

place: USA (Minnesota)
microorganism: Streptococci
disease manifestation: nosocomial infections
resistance: penicillin g
number sick: 350

date: 1977
place: USA (St. Paul)
microorganism: Staphylococcus aureus
disease manifestation: nosocomial infections
resistance: methicillin, aminoglycosides
number sick: 201

date: 1983
place: USA (Virginia, Florida)
microorganism: Staphylococcus aureus
disease manifestation: nosocomial infections
resistance: methicillin
number sick: 32

date: 1986
place: USA
microorganism: Shigella sonnei
disease manifestation: nosocomial infections
resistance: ampicillin, tetracycline, sulfamethoxazole/ trimethoprim
number sick: 347

date: 1988
place: Mexico
microorganism: Serratia marcescens
disease manifestation: nosocomial infections
resistance: ampicillin, carbenicillin, cefuroxim, netilimicin, gentamicin, tmp/smx, amikacin, phosphomicin
number sick: 80

date: 1989-1990
place: India
microorganism: Salmonella typhi
disease manifestation: diarrhea
resistance: chloramphenicol, ampicillin, tetracycline, streptomycin
number sick: 37

date: 1990-1992
place: USA
microorganism: Mycobacterium tuberculosis
disease manifestation: tuberculosis
resistance: multiple drugs
number sick: 142

date: 1991-1992
place: USA (New York)
microorganism: Enterococcus faecium
disease manifestation: diarrhea
resistance: vancomycin, ampicillin, gentamicin, streptomycin
number sick: 7

date: 1992
place: Philadelphia, New York, London
microorganism: Enterococcus faecalis, Enterococcus faecium
disease manifestation: diarrhea
resistance: vancomycin
number sick: 37

date: 1992
place: Spain
microorganism: Staphylococcus aureus
disease manifestation: nosocomial infections
resistance: methicillin, aminoglycosides
number sick: NA

date: 1992
place: USA
microorganism: Serratia marcescens
disease manifestation: nosocomial infections
resistance: multiple drugs
number sick: 12 infants born prematurely

* * *

Figure 5. Resistances to a number of antibiotics are transferable in bacteria.

antibiotic: beta-lactams, aminoglycosides, chloramphenicol, erythromycin, tetracycline
resistance mechanism: chemically modified by enzymes

antibiotic: tetracycline, erythromycin
resistance mechanism: actively removed from cell

antibiotic: erythromycin
resistance mechanism: enzymatic modification of target

antibiotic: beta-lactams, fusidic acid
resistance mechanism: proteins bind to and sequester antibiotics within target cell

antibiotic: sulfonamides, trimethoprim
resistance mechanism: synthesis of enzymes insensitive to the action of the drug

* * *

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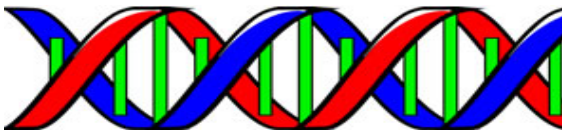
Genetics Science Learning Center
.....Name_____

Objective: Students will browse the Genetics Science Learning Center Website to learn about basic genetics, including the structure of DNA, transcription and translation.



Answer the questions as you browse through the site topics.

Site Location: http://learn.genetics.utah.edu/

Click on the link that says "Learn Genetics".

What is DNA? – Click on link “Tour of Basic Genetics”

2. What does DNA stand for?
_____
3. Why is DNA called a blueprint?
_____
4. The "twisted ladder" shape of the DNA molecule is called a _____ _____
5. Name the four bases found in a DNA molecule:
_____
6. A DNA strand is made of _____ which make up _____ which make up sentences.
7. These "sentences" are called
_____

What is a Gene? “Tour of Basic Genetics”

8. What is a gene?
_____
9. Blood cells use a protein called _____ to capture and carry oxygen.
10. When a gene is changed, it is said to be
_____
11. A mutation in the hemoglobin gene causes what disorder:
_____
What is a Chromosome?
12. If you stretched out all the DNA from a single cell, how long would it be??
_____
13. How many chromosomes are in a human cell? _____ a mosquito? _____ a carp? _____

What is a Protein? “Tour of Basic Genetics”

14. How is a protein like a car engine?

_____

15. Receptor proteins are responsible for picking up

_____

16. Each gene in DNA encodes information on how to make a

_____

17. Once in the cytoplasm, the _____ reads the message.

What is Heredity? “Tour of Basic Genetics”

18. The passing of traits from parents to child is the basis of

_____

19. Every child receives_____ of its chromosomes from his mother and half from his _____

20. When a sperm and egg join, they create a single cell called a

_____

21. Each child inherits a _____ set of chromosomes.

What is a Trait? “Tour of Basic Genetics”

22. Give an example of a physical trait:

_____

23. A dog fetching a bone is an example of what kind of trait?

_____

24. Scientists describe the set of information for each form of trait as an

_____

Build a DNA Molecule -Return to main menu and click on “Molecules of Inheritance”

25. Build a DNA molecule. What is the base pair rule?

_____

26. Draw the DNA molecule you built. Show how the bases are lined up and how they are attached.

"Transcribe and Translate a Gene" (right hand side)

27. Define transcription:

_____

28. Define translation:

_____

29. Follow the instructions for the activity. List the amino acid sequence you created.

_____
_____

"What Makes a Firefly Glow" (right hand side)

30. Fireflies glow to attract a _____ and to avoid _____
31. RNA polymerase binds to the _____ gene.
32. When transcription is complete, the LUC mRNA moves to the _____
33. The ribosome interprets the mRNA to produce a string of _____
34. In order to become a functioning luciferase enzyme, the string must _____
35. The enzymes bind to _____to create light.

For the following questions, you will use the site – www.dnai.org Click on the heading **"Applications"**.

Answer the following questions in complete sentences. Be sure to view the entire section to completely understand the questions being asked.

Part 1 Click on **"Human Identification"**. Read through the information given and then click on the heading **"Profiling"**.

36. How can one obtain a DNA fingerprint?

Click on **"DNA Variations and Fingerprints"** Read information and then click on the capital "A" for **"DNA Variations"**. Read and answer the following questions.

37. What are polymorphisms and what are they used for?

38. What is the difference between VNTR's and STR's?

Part 2 Click on the heading **"Family"**. Read the case "Sarbah vs Home Office, Ghana Immigration case 1985". Then, click on the capital "A" – **"Try the Comparison"** and answer the following questions.

39. How did Alec Jefferies help Christina?

40. What did Alex Jefferies do?

41. What was the result?

42. How did Jefferies compare the father's DNA and what was the result?

Part 3 Click on the heading **"Innocence"**.

43. What is the innocence project?

44. Describe the first case and its outcome.

Part 4 Go to **"Choose Another Module"** and click on **"Genes and Medicine"**. Click on **"Gene Testing"** and go to **"Making a Pedigree"**.

45. What are pedigrees used for?

46. How many generations are represented in the given pedigree?

47. Which genetic mutation is being tracked?

48. Who is the original carrier for this defective gene?

49. How many girls inherited this defective gene?

50. How can one benefit from this knowledge?

Part 5 Click on **"Gene Targeting"** then click on **"Animal Models"**.

51. Why are mice used in studying genetic disorders?

Click on **Mouse Models"**.

52. Why are mice good models?

But It’s Just a Bottle of Water…

by
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Part I—Moving In

On the first Mega-Store trip on move-in day at Midwest University, Sally and her mom picked up groceries for the dorm. Sally’s mom insisted on getting bottled water for her daughter because of her firm belief that bottled water was safer and cleaner than tap water. Back at the dorm, however, Sally’s new roommate, Jane, a sophomore Environmental Studies major, argued against this with facts she had learned in class.

“Did you know that while tap water is frequently tested to maintain public health and safety, bottled water has no guidelines for testing? The FDA can’t regulate water that is bottled and sold within the same state, which accounts for 60–70% of bottled water.”

Sally was taken aback by her new roommate’s comments on the first day that they met. “Ummmm, ok, but it can’t be that bad,” she mumbled. Sally’s mother, on the other hand, admired Jane’s enthusiasm and passion for the environment, and her knowledge of bottled water.

“So what you’re saying is you want to pay a lot more for untested water sealed in bottles that are horrible for the environment, especially since people don’t recycle?” said Jane.

“Water bottles are convenient… anyway, I recycle… sometimes,” stuttered Sally.

Jane was appalled to hear that her new roommate didn’t recycle often. What kind of person was she? “Do you know what happens to the unrecycled water bottles?!” she asked.

Feeling momentarily brilliant, Sally spouted, “They go into landfills, of course.”

“Yes, landfills that are filling quickly,” snapped Jane. “We don’t have room for water bottles that could be recycled. When water bottles are thrown in the trash, not only do they fill landfills, but they also increase air pollution and help destroy our ozone layer. When they are incinerated with the regular trash, toxic fumes are emitted that are harmful to our health, and these include greenhouse gasses that are also harmful to the environment.”

“Okay, okay, you made your point; I’ll recycle my water bottles ALL the time,” muttered Sally.

“But you still won’t stop drinking bottled water! Do you know where the water comes from? A lot of companies get their water from aquifers, many of which are running low. Water bottle companies do bulk water exports, extracting groundwater at unsustainable rates. And did you know that once an aquifer is emptied or polluted, they are almost impossible to restore? Soon we will have some major water shortages.”

Sally was frustrated, already arguing with her roommate, but she realized that Jane made a good point, and was impressed with her knowledge. But she still wondered why we didn’t hear about these effects if they were so horrible, and what could they do about it anyway.

After meeting Jane, Sally’s mom wondered how the girls would get along this semester. She was also intrigued with the information she heard from Jane.

Two weeks later Sally’s mother was in the Mega-Store back in her hometown and reached for a case of bottled water. She hesitated and thought… “Should I really be buying this water if it’s so bad for the environment?”

Question

1. Should Sally’s mother buy the bottled water? Why or why not?

Go to Part II—Background

But It’s Just a Bottle of Water… by May, Kotke and Bomar

Part II—Background

The recent popularity of bottled water has brought about a multitude of interrelated environmental issues, of which most consumers are not aware. Bottled water costs $4–$6 per gallon when purchased over the counter, and is 500–1000 times more expensive than

municipal tap water, with no guarantee that the bottled water is safer that tap water. Not only does it cost a small fortune to purchase bottled water, there are numerous associated costs in recycling PET(E). PET(E), or polyethylene terephthalate, is a plastic resin and a form of polyester. PET plastic is labeled with the #1 code on or near the bottom of bottles and is commonly used to package soft drinks, water, juice, peanut butter, salad dressings, and oil, as well as cosmetics and household cleaners. Primary issues related to the production and consumption of bottled water include safety, recycling, and groundwater.

Safety

Safety of drinking water is regulated by different agencies. Bottled water that is sold in states other than the state in which it was bottled (interstate commerce) is regulated by the Food and Drug Administration (FDA) under the Federal Food, Drug, and Cosmetic Act and is considered a food product. Municipal tap water is regulated by the Environmental Protection Agency under the Safe Drinking Water Act of 1974. This Act established health-based standards for drinking water to protect against both naturally-occurring and man-made contaminants that may be found in drinking water.

It is estimated that between 25–60% of bottled water is actually just municipal tap water. Bottled water from municipal sources is usually safe from bacterial contamination since it is chlorinated. Bottled water from non-municipal sources often lacks any treatment, in exchange for the ability to have an "all natural" product. Many producers of bottled water also add additional minerals or flavorings in the water to create a unique taste.

Bottled water that does not come from municipally treated sources may contain coliform bacteria such as *Escherichia coli, Campylobacter, Proteus, Salmonella, Serrati,* and *Shigella*. Each of these bacterial contaminants represents potential human health risks. Other concerns have also arisen over protozoan parasites such as *Cryptosporidium.* These organismal contaminants potentially threaten immunocompromised individuals (the very young, the elderly and those with HIV/AIDS). Moreover, bottled water may contain heavy metals (e.g., lead and mercury) and/or organic pesticides (e.g., azatrine), often at levels in excess of state and federal standards.

Recycling

While recycling is required in many states and strongly encouraged by others, the evidence suggests that adequate recycling is not occurring—in California alone, 19 million bottles each day are not being recycled. Recycling of PET plastic across the country has decreased over the past 5 years, and only about 19% of the bottles actually get recycled. The remaining PET bottles and containers end up in landfills.

Eleven states have "bottle bills" requiring deposits (usually $0.05/container; Michigan is the highest with $0.10/container) for each bottle purchased, but many states with a bottle bill exclude noncarbonated beverages such as water. While it is clear that these bottle bills are efficient at reducing roadside litter and increasing recycling rates, bottled water (and other noncarbonated beverages) falls into an administrative loophole.

Groundwater

Most of all, people generally have no idea where their water comes from. Municipalities generally get their water from surface water sources; companies that that do not get their water from municipalities get their water from below-ground sources. While all bottled water is not alike, the rate at which water is currently being extracted makes water a potentially non-renewable resource.

There are many different types of bottled water. These differences are based on the source of the water and types of treatments the water may receive.

The types of bottled water listed below often come from municipal sources.

- *Purified water,* which is often distilled, deionized, or filtered (reverse osmosis), removing many of the contaminants that may exist.
- *Sparkling water,* which is water that has been treated and then has had CO_2 added to it.

Bottled water not coming from above ground municipal sources includes:

- *Spring water,* which comes from the surface release of an underground aquifer.
- *Well water,* which comes from an aquifer into which a well has been drilled and water is mechanically pumped to the surface.
- *Artesian* water, which comes from a confined aquifer between impervious layers of rock from which the water flows naturally to the surface.
- *Mineral water,* which contains naturally occurring dissolved solids (>250 parts per million, or ppm).

Many corporations, such as Perrier, have invested greatly in getting the highest quality water, usually looking for “artesian” wells from which to draw. Many scientists believe that there are indirect costs associated with the production and consumption of bottled water. The biggest issue is overuse of the aquifer, leading to reduced stream flow and habitat reduction in aquatic ecosystems. Perrier, for example, wanted to pump 500 gallons/minute over a 5-year period (about one cubic mile of water) from one Wisconsin aquifer—estimated to reduce local stream flow about 50%. This water, once removed and transported around the country, is lost to the local water cycle.

Aquifer recharge rates vary greatly, depending upon annual rainfall and the type of rock water must percolate through. But since this is an open system—water is being transported out of the aquifer—water becomes a locally non-renewable resource if the withdrawal rate exceeds the rate of recharge.

Questions

1. How can we make society more aware of the environmental problems associated with bottled water?
2. What will be the future impact on the environment if we continue to use bottled water like we do today?
3. Is bottled water better or healthier for you than tap water? Are there times when bottled water is essential? Are there times when it is not?
4. List three ways you can help solve the environmental problems caused by water bottles.