Developed by the Federation of American Societies for Experimental Biology (FASEB) to educate the general public about the benefits of fundamental biomedical research.

INSIDE this issue

Conquering Pain and Infection with Drugs from Nature’s Medicine Cabinet

Growing pains: medical science comes of age
1

Golden age of antibiotics
2

Microbial gene swaps
3

Building an arsenal
4

Aspirin’s second act
7

Morphine’s ongoing mystery
8

Managing addiction, alcoholism, and gastrointestinal woes
8

Stunning relief from a killer snail
10

Sipping the microbial soup
11

Continuing, urgent needs
12
Acknowledgments
Conquering Pain and Infection with Drugs from Nature’s Medicine Cabinet

Author, Cathryn M. Delude

Scientific Advisor, David Newman, DPhil, National Cancer Institute, National Institutes of Health

Scientific Reviewer, John Beutler, PhD, National Cancer Institute, National Institutes of Health

BREAKTHROUGHS IN BIOSCIENCE COMMITTEE

James E. Barrett, PhD, Chair, Drexel University College of Medicine

David Brautigan, PhD, University of Virginia School of Medicine

Cherie L. Butts, PhD, United States Food and Drug Administration

Rao L. Divi, PhD, National Cancer Institute, National Institutes of Health

Marnie Halpern, PhD, Carnegie Institution of Washington

Tony E. Hugli, PhD, Torrey Pines Institute for Molecular Studies

Edward R. B. McCabe, MD, PhD, University of California Los Angeles

Loraine Oman-Ganes, MD, FRCP(C), CCMG, FACMG, RBC Life Insurance Company

Sharma S. Prabhakar, MD, MBA, FACP, Texas Tech University Health Sciences Center

Paula Stern, PhD, Northwestern University

BREAKTHROUGHS IN BIOSCIENCE PRODUCTION STAFF

Managing Editor, Tyrone C. Spady, PhD, Senior Science Policy Analyst, FASEB Office of Public Affairs

Production Staff, Lawrence Green, Communications Specialist, FASEB Office of Public Affairs

COVER: Seventy percent of our drugs for pain and infection are either derived from or inspired by natural products of rainforests and other ecosystems. These medicinal compounds have dramatically improved quality of life and significantly extended the human lifespan. Through decades of basic research to identify new drugs and unravel the underlying mechanisms of action, researchers are developing newer, more powerful therapies. Image credits: Tyrone C. Spady and Shutterstock Images.
Conquering Pain and Infection with Drugs from Nature’s Medicine Cabinet

Imagine a cave man, worse for wear after tussling with a mastodon. Having no corner drugstore, he stagers to a plant reputed to relieve pain. Perhaps he chews the leaves or bark, or steeps them in water and drinks the infusion. Perhaps he mixes a mud compress to keep his wound from festering. Such techniques for the medicinal uses of natural products would eventually be described on a 1,500 BC Egyptian papyrus and in ancient texts from China and Sumeria.

Throughout the ages and across continents, people have turned to natural sources of medicine. This practice continued as chemists learned to extract medicinal compounds from natural sources in the development of drugs, laying the foundation for the modern pharmaceutical industry. The first of these drugs were for the conquest of pain and infection, many of which became clinical breakthroughs almost immediately. Today, about 70% of our drugs for pain and infection are either derived from natural products or are inspired by them, including some introduced in the last decade. Together, analgesics and antibiotics have dramatically improved quality of life and significantly extended the human lifespan.

Studying the natural compounds that led to these drugs allows modern scientists to determine how the older drugs work and modify them to enhance their functional design and effectiveness — and to find entirely new classes of medically active compounds in nature. That is important, because we badly need newer and better drugs to solve our current crises with antibiotic-resistant “superbugs,” to prevent pandemic viral infections, and to ease intractable pain in cancer patients, for example.

In this article, we begin by looking at the first commercial drugs to be developed, the pain medications morphine and aspirin and their related compounds. Then we follow the discovery of antibiotics to more recent findings about our own cells and their interactions with the microbial world. Turning to the elucidation of the mechanisms of the first commercial pain medications, which occurred many years following their development, we discuss how those investigations led to new treatments for addiction and alcoholism — and heart disease. From there we consider the most recent discoveries in the natural world, including in the deep ocean and extremely hot, cold, or otherwise inhospitable environments.

Growing pains: medical science comes of age

People had used opium poppy for at least 6,000 years when in 1806 a German apothecary purified a colorless crystal from dried poppy resin with 10 times the narcotic, sleep-inducing potency of opium. It became known as morphine, used by doctors for relieving severe pain. Morphine was the first commercial pure natural product, introduced by the German company E. Merck in 1899. Later, researchers determined morphine’s chemical structure and synthesized it. Eventually, they used chemistry to modify and improve the molecule. Then researchers developed derivatives like oxycodone and oxycontin, which are semi-synthetic drugs based on structural modifications of morphine.

The further development of morphine ultimately established a new method for studying the medicinal properties of natural products with controlled studies of defined doses. Its purification helped to jump-start the modern pharmaceutical company and led to the isolation of similar (alkaloid) compounds — strychnine,
Breakthroughs in Bioscience

quinine, caffeine, and nicotine – from natural products.

Aspirin has a similar storyline. Ancient Sumerian clay tablets described the bark of willow trees as a remedy for pain and fever. Aspirin (acetylsalicylic acid), the drug derived from willow bark, made its pharmaceutical debut in 1889 as the first semi-synthetic drug based on a natural product. It was introduced by the German dye company Friedrich Bayer & Co., and is among the most successful and widely used drugs of all time.

By the mid 1900s, though, scientists had not yet explained how aspirin and morphine work to dull pain, or why they cause unwanted side effects: stomach ulcers with aspirin, and nausea and constipation (and addiction, dependence, and tolerance) for morphine. Meanwhile, researchers discovered that microorganisms, such as molds and bacteria, offered a versatile new source for medicines to treat deadly infections.

Golden age of antibiotics

The ancient Egyptians and Chinese used molds to treat infected wounds, but it took modern chemistry to link the antibacterial properties of mold to the treatment
of disease. In the late 1800s, Robert Koch proposed the “germ theory of disease” after demonstrating that microorganisms cause infectious diseases. That theory sent scientists hunting for natural products that kill pathogenic microbes. Among them, Alexander Fleming serendipitously discovered in 1928 that a blue-green mold, Penicillium notatum, killed colonies of the bacterium (Staphylococcus aureus) that causes pneumonia, staph infections, meningitis, and sepsis. By growing the mold in a pure culture, he enabled the isolation of penicillin about 10 years later. This first modern antibiotic has probably saved the most lives of any drug to date.

The discovery of penicillin revolutionized medicine and led to extensive screening of bacteria and molds for anti-infective activity and later for other biological activity. Microbe hunters and their associated chemists discovered new antibiotics, including streptomycin for treating tuberculosis. They also developed the semi-synthetic penicillin, methicillin, for Staphylococcus aureus infections.

To meet the instant demand for these “wonder drugs,” researchers used fermentation to turn the antibiotic-producing microbes (or mutated versions of them) into mini-factories. The microbes, grown in large vats with nutrients, churn out the antibiotic, which is then purified.

Thanks largely to these antibiotics, soldiers survived their wounds. The rate of women dying from infections following childbirth plummeted. Children succumbing to strep throat and scarlet fever became distant memories. Tuberculosis clinics began closing their doors. When microbes became resistant to existing antibiotics, a new one was usually added to the arsenal.

**Microbial gene swaps**

Microbes also have a devi- ous ability to swap genes like so many trading cards. Unlike our cells, bacteria keep some of their DNA separate from their chromosomes, packaged in tiny circles called plasmids. Plasmids move easily from one bacterium to another, even to members of different species. Many genes for virulence and resistance reside

Figure 1 — The serendipitous discovery of penicillin: British biologist Alexander Fleming was growing bacteria culture dishes in 1928 when a spore of a blue-green mold, the filamentous fungus Penicillium notatum, must have floated onto a plate of the disease-causing bacterium, Staphylococcus aureus. He noticed a clear circle where bacteria died, and then determined that the mold was producing a compound that killed the bacteria. That compound was penicillin, the first antibiotic. Source: Don Stalons, Centers for Disease Control and Prevention.

Figure 2 — Helping the war effort: Alexander Fleming proposed that penicillin might have therapeutic value if it could be produced in larger quantities. During World War II, that work was taken to the US, where collaborators developed fermentation methods to produce enough of what seemed a miracle drug in time to treat soldiers wounded in the D-Day invasion of Normandy. Source: Textbook of Bacteriology.
in these microbe-hopping plasmids, teaching other bacteria how to resist an antibiotic before ever being exposed to it. That poses a huge problem today as we encounter more virulent and multi-resistant microorganisms in our hospitals, homes, farms, and foods.

However, the discovery of plasmids was a boon to science and the foundation of recombinant DNA technology and genetic engineering. Scientists use plasmids as delivery vehicles to transfer genes into a living cell, including modified genes designed to make medicines. For example, this method is used in *E. coli* and yeast cells to produce insulin, for treating diabetes.

Plasmids are used to produce the anti-malaria drug artemisinin by transferring genes from the plant *Artemisia annua* to yeast, and to produce shikimic acid, a new drug used to combat influenza infections and made with the help of genes copied from the star anise plant. Employing microbes to produce plant compounds spares the plants themselves, which in some cases are rapidly becoming endangered due to massive over-harvesting.

**Building an arsenal**

By understanding the tricks microbes use to evade our antibiotics, scientists have designed antibiotics less prone to resistance. For example, modifying the structure of part of the tetracycline antibiotic, which was discovered in a soil microbe, overcomes the pump that bacteria use to expel the drug. This modified

---

**Figure 3 — How bacteria develop resistance:** Through the acquisition of specific genetic mutations, bacteria may develop resistance via one or more of the following mechanisms: degrading the antibiotic, altering the antibiotic such that it is rendered inactive, or pumping the drug out of the cell (efflux). We also encourage bacteria to use such wily tricks when doctors overprescribe antibiotics, such as for minor infections that will heal on their own or for viral infections like colds or the flu (antibiotics do not kill viruses), or when patients misuse antibiotics by not taking the full course of treatment. Adapted from the Encyclopedia of Surgery by Corporate Press.

---

**Crimes of Slimes**

In the past two decades, scientists have realized that slimy bacterial formations called biofilms underlie many persistent infections. Biofilms are complex communities of diverse microbial species that secrete a protective film that is impervious to antibiotics and disinfectants. These films form throughout nature, and also on hospital catheters and medical implants, in infected ear canals, and in the mucus-clogged lungs of patients with cystic fibrosis. Naturally, scientists want to overcome these microbial defenses against our anti-infectives.

To form biofilms, microbes communicate with each other using cell-to-cell signaling molecules. This signaling may orchestrate the transition of harmless microbes in our body into pathogenic ones. Microbes may keep a low profile and wait until they sense a quorum of comrades before launching an attack on the host cells. To defend themselves from these microbes, some organisms produce compounds that scramble these communication signals. Scientists are screening such compounds for new approaches to prevent biofilms from forming on medical implants and human tissues and to keep the bacteria in our bodies from becoming pathogenic.

Likewise, frogs and other amphibians that live in moist and murky places secrete rich cocktails of antimicrobial compounds to protect their skin from bacteria and fungi—an inspiration for future anti-fungals and other treatments.
natural product, called Tygacil (tigecycline), was approved in 2005 as a broad-spectrum antibiotic against many resistant bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA).

How do researchers build a better drug based on a natural product? The blueprint often calls for finding the compound’s “base scaffold” or pharmacophore (the active part of the molecule that binds to other molecules) and then improving it. For example, for the semi-synthetic antibiotic Vibativ (telavancin), approved in 2009, researchers structurally modified the scaffold of vancomycin, which is derived from a microbe found in the soil of the remote jungles of Borneo, so it better inhibits a bacterium’s ability to assemble its cell wall.

Combining scaffolds from two different natural products also produces more resistant antibiotics. One example is TD-1792, which splices the scaffolds of vancomycin and fungus-based cephalosporin, which work at different targets in bacteria, for treating MRSA and other very resistant strains.

In the early days, scientists had better luck developing drugs against bacteria than against viruses and fungi. But once researchers discovered mechanisms that viruses use to infect and take over the host cell, they were able to develop antiviral compounds. These include reverse transcriptase inhibitors like azidothymidine (AZT) that prevent the HIV virus from tricking our cells into making HIV DNA. Such inhibitors often mimic the structure of a DNA or RNA component, called a nucleotide, to prevent that component from functioning in the virus. Another strategy is to foil the HIV protease, an enzyme that normally cleaves HIV peptides into functional proteins. Protease inhibitors mimic the structure of the site where that cleavage occurs, thus preventing viral replication. These breakthroughs led to many similar drugs that have allowed HIV/AIDS patients to live long, productive lives. The past decade has also introduced new antiviral drugs, including several to treat hepatitis B, one of our most common persistent viral infections.

Fungal infections pose a real challenge compared to those caused by bacteria because of greater similarity between cells of fungi and our own, so antifungal agents often have more side effects. Until recently, there was little doctors could do to treat or prevent the raging fungal infections that can kill people with suppressed immunity, whether from cancer or treatments to prevent the body from rejecting transplant organs or stem cells, or from HIV/AIDS. The main options were two very old natural product drugs (griseofulvin and amphotericin B, isolated from a mold related to the source of penicillin and a soil bacterium, respectively), which though effective had severe and sometimes lethal side effects, or a class of synthetic antifungals known as “azoles.” But just as with the antibacterial agents, resistance mechanisms rapidly occurred leading to another arms...
Much of recent drug research focuses on synthetic chemistry—forming more complex chemical compounds from simpler substances—and "rationally designed" compounds intended to interact with a specific molecule in our body. But natural sources continue to prove just as valuable when combined with newer genetic and molecular technologies. Here are the new anti-infective drugs approved worldwide since 2000.

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Trade name</th>
<th>Generic name</th>
<th>Source</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural Product</td>
<td>Cubicin</td>
<td>daptomycin</td>
<td>Soil bacterium</td>
<td>Skin infections</td>
</tr>
<tr>
<td></td>
<td>Ketek</td>
<td>telithromycin</td>
<td>Soil bacterium</td>
<td>Bacterial pneumonia</td>
</tr>
<tr>
<td></td>
<td>Omegacin</td>
<td>biapenem</td>
<td>Pair of fungi</td>
<td>Septic shock; broad-spectrum antibiotic</td>
</tr>
<tr>
<td></td>
<td>Invanz</td>
<td>ertapenem sodium</td>
<td>Same as above</td>
<td>Severe infections</td>
</tr>
<tr>
<td></td>
<td>Finibax</td>
<td>doripenem</td>
<td>Same as above</td>
<td>Ultra-broad spectrum antibiotic</td>
</tr>
<tr>
<td></td>
<td>Tygacil</td>
<td>tigecycline</td>
<td>Soil bacterium</td>
<td>MRSA</td>
</tr>
<tr>
<td></td>
<td>Altabax</td>
<td>retapamulin</td>
<td>Fungus</td>
<td>Impetigo caused by MRSA</td>
</tr>
<tr>
<td></td>
<td>Zeftera</td>
<td>ceftobiprole medocaril</td>
<td>Fungus</td>
<td>Complicated skin infections</td>
</tr>
<tr>
<td></td>
<td>Vibativ</td>
<td>telavancin HCl</td>
<td>Soil bacterium from rainforest of Borneo</td>
<td>Resistant infections</td>
</tr>
<tr>
<td></td>
<td>Cancidas</td>
<td>caspofungin acetate</td>
<td>Fungus</td>
<td>Fungal infections that involve the stomach, lungs, esophagus, or other internal body areas</td>
</tr>
<tr>
<td></td>
<td>Fungard/Myccamine</td>
<td>micafungin sodium</td>
<td>Fungus</td>
<td>Yeast infections in cancer, organ or stem cell transplant, and AIDS patients</td>
</tr>
<tr>
<td></td>
<td>Eraxis</td>
<td>anidulafungin</td>
<td>Fungus</td>
<td>Invasive fungal infections</td>
</tr>
<tr>
<td></td>
<td>Fuzeon</td>
<td>enfuvirtide</td>
<td>Synthetic version of a viral peptide (short strand of amino acids)</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>PeramiFlu</td>
<td>peramivir</td>
<td>Modeled on an enzyme derived from the star anise plant</td>
<td>Influenza (including H1N1 flu)</td>
</tr>
<tr>
<td></td>
<td>Viread</td>
<td>tenofovir disoproxil fumarate</td>
<td>Prodrug* of tenofovir</td>
<td>Chronic hepatitis B virus</td>
</tr>
<tr>
<td></td>
<td>Valcyte</td>
<td>valganciclovir</td>
<td>Prodrug* for ganciclovir</td>
<td>Cytomegalovirus infections in kidney, heart, and pancreas transplant patients</td>
</tr>
<tr>
<td></td>
<td>Hepsera</td>
<td>adefovir dipivoxil</td>
<td>Derived from the nucleotide adenine</td>
<td>Hepatitis B and herpes simplex virus infection</td>
</tr>
<tr>
<td></td>
<td>Emtriva</td>
<td>emtricitabine</td>
<td>Derived from the nucleotide cytosine</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Baraclude</td>
<td>entecavir</td>
<td>Derived from the nucleotide guanine</td>
<td>Hepatitis B symptoms</td>
</tr>
<tr>
<td></td>
<td>Sebivo</td>
<td>telbivudine</td>
<td>Derived from the nucleotide thymine</td>
<td>Chronic hepatitis B</td>
</tr>
<tr>
<td></td>
<td>Intelence</td>
<td>etravuclid</td>
<td>Modeled on the common structural components of cytosine and thymine</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Kaletra</td>
<td>lopinavine</td>
<td>Modeled after an HIV protease enzyme</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Reyataz</td>
<td>atazanavir</td>
<td>Similar to above</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Lexiva</td>
<td>fosamprenavir</td>
<td>Similar to above</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Aptivus</td>
<td>tipranavir</td>
<td>Similar to above</td>
<td>HIV-1 infection</td>
</tr>
<tr>
<td></td>
<td>Prezista</td>
<td>darunavir</td>
<td>As with other HIV protease inhibitors, a 3D mimic of the natural substrate</td>
<td>HIV-1 infection</td>
</tr>
</tbody>
</table>

*Prodrugs are pharmaceuticals that are administered in an inactive form, which then must be metabolized by the body to produce the medicinally active compound. Prodrug forms help more medicine reach its target by generally improving absorption and/or specificity.
race. Working with natural scaffolds/pharmacophores has led to three sorely needed antifungals in the past 10 years. All have a similar mechanism of action, attacking a part of the fungus that is different from the human cell. These are also approved for children and babies, who often have acquired fungal infections from their HIV-infected mothers and who have had few possibilities for treatment. The new antifungals now have a huge worldwide market, which will probably increase as more patients in high-risk categories (immunocompromised and pediatric) are treated with these agents.

In addition to leading to new drugs, understanding the nature of antibiotic resistance and the spread of other infections has changed clinical practice. Knowing how readily bacteria can acquire resistance genes and how impervious some bacteria are to anti-infectives has led to more vigilant hygiene policies to prevent hospital-acquired infections. Also more physicians are aware of the need to reduce the overuse and misuse of antibiotics.

Aspirin’s second act

As penicillin was making its medical debut, scientists were still trying to understand how aspirin works—and how to improve it. In 1946, NIH researcher Julius Axelrod was looking for an analgesic that had the pain and fever relief of aspirin, without its risk of causing stomach ulcers, bleeding, and occasionally kidney damage. He discovered that a byproduct of aspirin in the blood, acetaminophen (Tylenol is one of many brands), reduces pain and fever. (We now know that acetaminophen can cause liver damage.)

But what was the mode of action for aspirin and acetaminophen? The answer emerged in 1971, when British researcher Sir John Vane discovered that aspirin inhibits a family of proteins called cyclooxygenase (COX-1 and 2) enzymes. These enzymes drive the production of prostaglandins, a group of hormone-like substances derived from fatty acids that cause pain, inflammation, and fever. By inhibiting an early stage in the complicated pathway that produces various prostaglandins, aspirin reduces pain and inflammation.

Later, researchers discovered that prostaglandins also affect platelet formation and the relaxation of the smooth muscle cells that line blood vessels. By reducing prostaglandins, aspirin prevents platelets in the blood from sticking together to form clots, including those that cause heart
attack and stroke. Acetaminophen acts further down the COX-2 pathway and does not affect platelets.

The discovery that aspirin prevented platelets from sticking initiated a second renaissance for aspirin as a preventive for heart attack and stroke. Ironically, in 1920 Bayer had to assure people that aspirin “Does not affect the heart” to allay fears that it damages heart muscle. In 1948, a California doctor recommended that his patients take an aspirin a day to reduce the risk of heart attack—but without evidence of a protective mechanism no one paid much heed. Now, 80 million people take a “baby” dose of aspirin to reduce risk of heart disease and stroke (although some people may still experience intestinal bleeding with that dose.)

Reducing systemic inflammation is increasingly seen as important not just in preventing cardiovascular disease, but also in reducing harm from diabetes, cancer, and even Alzheimer’s disease—a few of the expanding clinical applications for this old natural product remedy.

Meanwhile, pharmaceutical companies want to make stronger COX-2 inhibitors to better control pain and inflammation. Some first-generation drugs, like Vioxx, were withdrawn because they actually can harm the heart in some patients. But several drugs in the pipeline may not have these side effects. One of them, etoricoxib, has a large market in Europe and is under consideration by the FDA in the United States.

**Morphine’s ongoing mystery**

How morphine works took longer to understand, even after it was synthesized in 1952. Clearly, morphine acts on the brain, but why would our brains have receptors for it? Could morphine be mimicking something similar to what our bodies already produce?

Researchers knew that for our brains to detect morphine, the compound must activate a protein receptor on our neurons. Brain cells communicate by releasing chemical signals, called neurotransmitters, which then attach to specific receptors on neighboring neurons, like a key fitting into a lock. By 1952, few receptors in the brain had been characterized. In 1972, the National Institute of Mental Health encouraged researchers to do basic research on the brain, and the next year researchers identified a receptor for morphine and related opioid chemicals.

They soon discovered natural opiates that both animal and human brains release as a natural analgesic in response to pain—endorphins and related compounds called enkephalins. These compounds can fold so that they have a similar 3-D structure to that of morphine. Having this innate pain control mechanism makes sense, since it allows an animal in danger to ignore pain long enough to escape a predator.

In the 1990s, researchers began to clone the opioid receptors, study their genes, and create molecular probes to identify the locations of receptors in cells. They found constellations of different opioid receptors, divided into four major groups with many subtypes, in diverse regions of the brain, spinal cord, peripheral nerves, and gut. (Only the “mu” opioid receptors in the brain are associated with addiction and abuse.)

These wide-ranging locations and multiple receptor types implied that natural opioids play a more nuanced role in our behavior than just pain control, extending to our immune responses, appetite, sleep, reproduction, and our pleasure- and reward-seeking behavior. Our brain releases endorphins, for example, when we eat or do other life-sustaining activities that our brain’s reward circuit reinforces.

We still have much to learn about these receptors, how they respond to both our own and foreign opiates, and how they function in the body. Why, for instance, does an addicted person develop tolerance to morphine, needing larger doses to achieve the same high? Tolerance is also a medical problem for people in chronic severe pain, such as from arthritis, cancer, neuropathy, or fibromyalgia, who may need progressively larger doses to obtain relief.

**Managing addiction, alcoholism, and gastrointestinal woes**

Despite many unanswered questions, studying the opioid system enabled several treatments for addiction and alcoholism. Early on, the synthetic opiate metha-
done was developed for opiate addiction. It allows the opiate receptors to signal a morphine-like “high” but more gradually, without the euphoric “rush” that leads to craving. The first treatment for alcoholism was naltrexone, approved in 1995 and marketed as Depade, ReVia, and Vivitrol. It fills the opioid receptor’s lock with a fake key so the opioid molecule cannot trigger a euphoric response.

For patients in pain, such as those following surgery or suffering from terminal cancer, morphine remains the most effective analgesic. However, because morphine also activates opioid receptors in the intestines as well as in the brain’s pain pathways, the bowels slow down, causing constipation that can become so problematic patients cannot continue morphine. Interestingly, Imodium (loperamide) counters diarrhea by activating opioid receptors in the large intestine—which slows down the unwanted movement. It only acts peripherally, with a diminished effect on the brain.

Understanding these effects led to recent treatments for morphine-induced constipation. The opioid-mimic Relistor (methylnaloxone or MNTX), introduced in 2005, was designed to work selectively only in the intestines and not enter the brain. It occupies the spot for morphine at the opioid receptors in the intestine, which keeps the bowels moving and allows patients to continue taking morphine. A similar molecule introduced in 2008, Alvimopan (entereg), is designed

Figure 6 — How naltrexone helps alcoholics; The drug naltrexone was designed to manage alcohol dependence. Alcohol releases natural opioids from nerves. These opioids bind to receptors on neighboring neurons, producing a euphoria that makes vulnerable people want to drink more alcohol. Naltrexone mimics the natural opioid structure and blocks their action by binding to the receptors without causing euphoria. Reprinted with permission from the Society for Neuroscience.
for patients following bowel surgery. Currently, these compounds have restricted use, but researchers are developing other compounds for opioid-induced constipation that may have wider application.

Still, the problem remains that morphine and its analgesic derivatives like oxycodone and oxycontin have addictive properties and also lead to tolerance. But solutions may be lurking in the natural world where people never thought to look or even in long-used remedies that were too complex to study scientifically until quite recently.

**Stunning relief from a killer snail**

The marine environment is a huge but largely untapped source of natural products for drug development. Oceans cover 70 percent of the earth’s surface and are home to weird organisms producing bizarre compounds for defending themselves, hunting prey, and thriving in salty, cold, dark depths or hot, sulfuric seas. The first drug developed from a marine source is emblematic of the treasure trove of potential medicines from under the sea.

Growing up in the Philippines, Baldomer Olivera was fascinated with fish-hunting marine cone snails that use their venom to stun prey. Their sting, it was said, could kill a man so fast he would just have time to smoke a cigarette.

Early in his career in the late 1960s, Olivera injected the venom of one of these snails, *Conus geographus*, into the abdomens of mice, which immediately paralyzed them. Wanting to pinpoint the active compound, he chemically separated the various peptides in the venom, a process called fractionation, and injected the separated compounds one by one in mice abdomens. Surprisingly, not just one, but many peptides acted as potent nerve toxins.

Fast forward to 1972 when an undergraduate student in Olivera’s lab at the University of Utah injected the toxins in the central nervous system of mice. Each toxin had a very specific effect, sometimes also acting differently in young and old mice. They learned that each toxin blocks a different pore, or channel protein, that lets charged particles such as calcium, sodium, and potassium ions pass in and out of cells. Blocking the channel disrupts the relay of messages between brain and body.

Thus, the toxins were exquisitely selective, like smart drugs. For example, the calcium blockers that treat hypertension act throughout the body, while the snail toxin ziconotide (now the drug Prialt) targets just the calcium channels in nerves, thus blocking pain signals to the brain.

Animal tests showed that this toxin had 1,000 times the analgesic power of morphine, but it did not lose potency or lead to tolerance with prolonged use. After decades of support from the NIH National Institute of General Medical Sciences to Dr. Olivera and his colleagues and the synthesis of this compound in the late 1980’s, Prialt entered clinical trials for treating pain in terminal cancer and AIDS patients, and was later expanded to other patients with intractable pain. It received FDA approval in 2004 – the first drug derived directly from a marine organism that required no modification or improvement to work. Currently, it needs to be delivered through an implanted catheter, but oral versions of similar cone snail toxins are being developed that could make such a powerful, non-addictive, non-narcotic pain killer more widely available.

Snail toxins are also being explored for epilepsy, cardiovascular disease, and neurological disorders. Some toxins target

---

Figure 7 — Marine cone snail: Marine cone snails (*Conus*) produce many toxins to stun prey or ward off predators. One such toxin was developed into a new powerful pain medication, Prialt (ziconotide), in 2004 that does not cause addiction or tolerance. Other toxins may lead to new treatments for epilepsy, cardiovascular disease, and neurological diseases. Image courtesy of Richard Seaman.
breakthroughs in bioscience

Receptors that are important for memory (N-methyl-D-aspartate or NMDA receptors). Others affect nicotinic acetylcholine receptors that help regulate muscle contractions, among other important functions. Other marine creatures also produce venomous cocktails of hundreds or thousands of toxins, so Prialt may be the tip of an iceberg containing new breakthroughs in managing diverse diseases.

**Sipping the microbial soup**

The oceans also host an unfathomably rich diversity of microorganisms that scientists are eager to explore for medicinal compounds—with activity not just against pain neurons but also against infections, inflammation, and cancer. Organisms thriving in seemingly inhospitable extreme environments like hot sulfur springs, acidic or alkaline pools, deep-frozen arctic ice, and parched desert sands, called “extremophile” organisms, also have unusual metabolisms and so may produce never-before-encountered compounds that could inspire new drugs.

Until recently, it was hard to study this microbial cornucopia because an estimated 99 percent of these microorganisms cannot be cultured under laboratory conditions. Now, these biological frontiers are open to explorers using new and emerging technologies combining microbiology, chemistry, genomics, and biosynthetic techniques.

Rather than coaxing these finicky microbes to adapt to life on a Petri dish, scientists can fish the DNA out of a sample of water, ice, or soil and then isolate genes from these samples and make many copies for genetic analysis. For this, researchers use PCR (polymerase chain reaction), which relies on the enzyme Taq polymerase—itself derived from an extremophile microbe discovered in a Yellowstone hot spring! This approach, called metagenomics, can identify the breadth of organisms in a sample and detect the existence of unknown organisms for further study.

Scientists scan these microbial soups for genetic sequences that appear to produce biologically active proteins. When they find one, they can insert it in a plasmid and transfer the gene to laboratory bacteria or yeast. Those “domesticated” microbes act like mini-factories and churn out the compound of interest.

Testing the activity of each product separately can turn up new candidates. Does a new gene product, perhaps, slow down the growth of the superbug MRSA? Does it enhance the activity of an opioid receptor? If so, scientists can use genetic engineering or chemical synthesis to modify the gene and/or the compound it produces and see if these changes improve the therapeutic function of the resulting chemical.

The flipside of investigating previously inaccessible environments is finding new horizons in the known world. Advanced isolation and identification processes are uncovering previously unknown compounds in long-used natural products. For example, the pinwheel flower (*Tabernaemontana divaricata*) has long been used for medicinal purposes in Asia. In 2004, researchers isolated conolidine, one of several non-opioid analgesic compounds in the plant, albeit in vanishingly small amounts. In 2011, researchers synthesized

---

Figure 8 — Hot springs teem with microbial life: The hot springs of Yellowstone National Park host many microorganisms that produce unusual proteins to help them withstand hot temperatures and highly acidic or alkaline conditions. These natural compounds have found uses in biotechnology and are being investigated for their medicinal value. *Image credit: Jim David.*
To Kill a Mosquito’s Parasites

“A handful of sweet wormwood (qinghao) immersed with two liters of water, wring out the juice and drink it all.” This recipe for a treatment of fevers in a 4th century Chinese text is vague. But reading it in 1971 gave Youyou Tu, the 2011 recipient of the Lasker Award for Clinical Medicine, the clue she needed to develop artemisinin, a breakthrough treatment for drug-resistant malaria that is estimated to save millions of lives annually – and saves many more malaria suffers from the debilitating fevers of the disease.

Malaria is caused by mosquito-borne parasites (Plasmodium) that infect some 225 million people and kill nearly a million people annually, according to the World Health Organization’s (WHO’s) World Malaria Report 2010. By the 1960s, many parasites were resistant to the main anti-malarial drugs, quinine (from the bark of the Peruvian cinchona tree) and its derivative chloroquine, and soldiers fighting in the Vietnam War were ravaged by malaria. China, a supporter of North Vietnam and in the throes of Chairman Mao Tse-tung’s Cultural Revolution, established a clandestine Project 523 to develop new antimalarial drugs in 1967.

Tapped for the project, Youyou Tu combed 5,000 years worth of ancient texts to find 2,000 recipes related to the malaria treatments and analyzed 380 extracts from more than 200 herbs. For the extract from the sweet wormwood bush (Artemisia annua), she intuited from the above recipe that the standard way of extracting herbal compounds using high heat rendered this unusual compound inactive. Using lower temperature, she showed that artemisinin was a potent anti-malarial compound. The Chinese developed artemisinin as a highly effective drug, but it was many years before the research was accessible outside of China. The mechanism by which it works is still unclear.

Recently, artemisinin has become WHO’s recommended treatment, but only in combination with other anti-malarial drugs (ACTs or artemisinin combined therapies including the 2009 FDA-approved Coartem) to prevent or delay artemisinin resistance. Still, the high cost of artemisinin limits ACT’s dissemination in malaria-infested Africa. To help reduce the price to $1 per pill for Africans, researchers are developing methods to produce artemisinin through large-scale fermentation of yeast, rather than the costly practice of harvesting the plant for extraction.

Conolidine, so they can now make enough of it to study—and perhaps modify it or use it as a model for a rationally designed chemical that could have selective effects on our pain pathways.

Continuing, urgent needs

We still have many gaps in our arsenal of medicines for both old and emerging diseases. Pandemic viral infections threaten us as never before, thanks to the global travel that brings once isolated infections to everyone’s door. HIV/AIDS continues to rage around the world. Tuberculosis is coming back, with drug resistance. Lyme disease and other tick-borne infections are spreading, and mosquito-borne Dengue fever and malaria are too. Millions of people still suffer from intractable pain so severe it causes economic loss and sometimes leads to suicide. Bacteria will soon find a way around even our newest, last-resort antibiotics. In addition, we also need new and better approaches for treating cancer, heart disease, autoimmune diseases, metabolic disorders, and a long roster of brain disorders.

The natural world remains a rich source of undiscovered medical compounds. Since life on earth began an estimated 3.5 billion years ago, organisms have been fine-tuning biological compounds to survive the changing onslaughts of the world. Perhaps nature has already come up with at least partial solutions to the problems we want to solve. Still, beneficial natural compounds may be hard to detect amongst the vast and varied molecules organisms use to survive. The molecules may be challenging to isolate from a fragile species with a bizarre life cycle. Or the organisms may live in inaccessible locations, like deep-sea vents. Once isolated, it may take years to synthesize a compound.

We now have more access to the enormous untapped potential of nature’s known and unknown niches on both land and sea. New genomic and molecular techniques, along with clever advances in engineering and chemistry, have expanded our horizons so that we can explore the medici-
nal bounty in natural products in search of new and better treatments for a long list of unmet medical needs. Going forward, we will need more basic discovery and technical innovations to continue to reap inspiration from the natural products that can heal what ails us.

**Note:** The coming issue of *Breakthroughs in Bioscience* will focus on naturally occurring compounds used to treat cancer.

---

**Additional suggested reading:**


Chivian, Eric and Aaron Berstein, *Sustaining Life: How Human Health Depends on Biodiversity* (Chapters 4-6), Oxford University Press, USA; III edition (June 2, 2008).


**Biographies:**

**Cathryn M. Delude,** of Andover, Massachusetts, writes about science and medicine for magazines and newspapers. She has written for FASEB in the past, and her articles have appeared in *Nature Outlook*, AACC’s Cancer Discovery, Los Angeles Times, Boston Globe, New York Times, Scientific American, The Scientist, Proto: Dispatches from the Frontiers of Medicine, and other publications on topics including neuroscience, cancer, molecular biology, microbiology, infectious diseases, water, energy, and civil and environmental engineering. She has additionally written for the Howard Hughes Medical Institute, Harvard Health Publications, Harvard School of Public Health, Massachusetts General Hospital, Massachusetts Institute of Technology, Dana Farber Cancer Center, Stowers Institute for Medical Research, and the National Institutes of Health - Office of Science Education.

**David Newman,** DPhil, is the current Chief of the Natural Products Branch (NPB) in the Developmental Therapeutics Program at the National Cancer Institute in Frederick, MD. Born in the United Kingdom, he received a MSc in synthetic organic chemistry and a DPhil for work in microbial chemistry. He came to the United States in 1968 as a postdoctoral researcher at the University of Georgia and in 1970 joined SK&F as a biochemicalist. In 1985, he left SK&F and, following work in marine and microbial discovery programs at various companies, he joined the NPB in 1991 with responsibilities for marine and microbial collection programs. In 2006 he was appointed to his current position. His research interests are in natural product structures as drugs and leads, and he has the authored of over 150 scientific articles, reviews, and book chapters, and holds 21 patents, mainly on microbial products.