Biodiversity: Its Importance to Human Health

Interim Executive Summary

A Project of the Center for Health and the Global Environment

Harvard Medical School

under the auspices of the World Health Organization and the United Nations Environment Programme

Editor
Eric Chivian M.D.
The project Biodiversity: Its Importance to Human Health
has been made possible through the generous support
of several individuals and the following foundations:

Bristol-Myers Squibb Company
Nathan Cummings Foundation
Richard & Rhoda Goldman Fund
Clarence E. Heller Charitable Foundation
Johnson & Johnson
John D. and Catherine T. MacArthur Foundation
The New York Community Trust
The Pocantico Conference Center of the Rockefeller Brothers Fund
V. Kann Rasmussen Foundation
Wallace Genetic Foundation
Wallace Global Fund
The Winslow Foundation
Biodiversity: Its Importance to Human Health

Interim Executive Summary

A Project of the Center for Health and the Global Environment
Harvard Medical School

under the auspices of the World Health Organization
and the United Nations Environment Programme

Editor
Eric Chivian M.D.

Associate Editors
Maria Alice dos Santos Alves Ph.D. (Brazil)
Robert Bos M.Sc. (WHO)
Paul Epstein M.D., MPH (USA)
Madhav Gadgil Ph.D. (India)
Hiremagular Gopalan Ph.D. (UNEP)
Daniel Hillel Ph.D. (Israel)
John Kilama Ph.D. (USA/Uganda)
Jeffrey McNeely Ph.D. (IUCN)
Jerry Melillo Ph.D. (USA)
David Molyneux Ph.D., Dsc (UK)
Jo Mulongoy Ph.D. (CBD)
David Newman Ph.D. (USA)
Richard Ostfeld Ph.D. (USA)
Stuart Pimm Ph.D. (USA)
Joshua Rosenthal Ph.D. (USA)
Cynthia Rosenzweig Ph.D. (USA)
Osvaldo Sala Ph.D. (Argentina)
Introduction

E.O. Wilson once said about ants “we need them to survive, but they don’t need us at all.” The same, in fact, could be said about countless other insects, bacteria, fungi, plankton, plants, and other organisms. This central truth, however, is largely lost to most of us. Rather, we act as if we were totally independent of Nature, as if it were an infinite source of products and services for our use alone, and an infinite sink for our wastes.

During the past 50 years, for example, we have squandered one fourth of the world’s topsoil, one fifth of its agricultural land, and one third of its forests, while at the same time increasing our population from 2.5 billion to over 6.1 billion. We have dumped many millions of tons of toxic chemicals onto soils and into freshwater, the oceans, and the air, while knowing very little about the effects these chemicals have on other species, or, in fact, on ourselves. We have changed the composition of the atmosphere, thinning the ozone layer that filters out harmful ultraviolet radiation, toxic to all living things on land and in surface waters, and increasing the concentration of atmospheric carbon dioxide to levels not present on Earth for more than 420,000 years. These carbon dioxide emissions, caused mainly by our burning fossil fuels, are unleashing a warming of the Earth’s surface and a change in the climate that will increasingly threaten our health, and the survival of other species worldwide. And we are now consuming or wasting almost half of all the planet’s net photosynthetic production on land and more than half of its available freshwater. Most disturbing of all, we are so damaging the habitats in which other species live that we are driving them to extinction, the only truly irreversible consequence of our environmental assaults, at a rate that is hundreds or perhaps even thousands of times greater than natural background rates. As a result, biologists are calculating, on the basis of habitat destruction alone, that as many as two thirds of all species on Earth could be lost by the end of this century, a proportion of lost species that matches the great extinction event, 65 million years ago, that wiped out the dinosaurs. That event was most likely the result of a giant asteroid striking the Earth; this one we alone are causing.

We have done all these things, our species, Homo sapiens sapiens, one species out of perhaps ten million, and a very young species at that, having evolved only about 130,000 years ago, behaving as if these alterations were happening someplace other than where we live, as if they had no effect on us whatsoever.

This mindless degradation of the planet is driven by many factors, not the least of which is our inability to take seriously the implications of our rapidly growing populations and of our unsustainable consumption, largely by people in industrialized countries, of its resources. Ultimately, our behavior is the result of a fundamental failure to recognize that human beings are an inseparable part of Nature and that we cannot damage it severely without severely damaging ourselves.

This report was first conceived ten years ago at the Earth Summit in Rio de Janeiro when the great promise of that event and its ambitious goals for controlling global climate change and conserving the world’s biodiversity were first elaborated. What was recognized then, and what is even more widely appreciated now, was that, in contrast to the issue of climate change, there was inadequate attention being paid to the potential consequences for human health resulting from species loss and the disruption of ecosystems. This general neglect of the relationship between biodiversity and human health, it was believed, was a very serious problem. Not only were the full human dimensions of biodiversity loss failing to inform policy decisions, but the general public, lacking an understanding of the health risks involved, was not grasping the magnitude of the biodiversity
crisis, and not developing a sense of urgency to address it. Unfortunately, aesthetic, ethical, religious, even economic, arguments had not been enough to convince them.

To address this need, the Center for Health and the Global Environment at Harvard Medical School proposed that it coordinate an international scientific effort to compile what was known about how other species contribute to human health, under the auspices of the World Health Organization (WHO) and the United Nations Environment Programme (UNEP), and to produce a report on the subject that would be the most comprehensive one available. Happily, both the WHO and UNEP agreed to this proposal.

What follows is the Interim Executive Summary for this report “Biodiversity: Its Importance to Human Health.” It is interim because the final report, to be published by Oxford University Press as a book written for a general audience, and the final Executive Summary for Policy-Makers based on that book, will not appear until late 2003. Other products from this project include a Technical Report that will be available on the Center’s website in 2004, and sections on health for the Millennium Ecosystem Assessment. Upon completion, the report will be presented to the WHO and UNEP, and to the U.N. Convention on Biological Diversity.

We have divided the project into seven working groups, each of which will produce a chapter, led by two co-chairs and composed of experts from industrialized and developing countries, and from a wide range of disciplines.

- Chapter 1 looks at the status of global biodiversity and examines the forces that threaten it.
- Chapter 2 summarizes ecosystem services that support all life, including human life, on this planet.
- Chapter 3 covers medicines and natural pesticides that are derived from plants, animals, and microbes.
- Chapter 4 traces the dependency of medical research on other species.
- Chapter 5 examines the complex relationships among ecosystem disruption, biodiversity, and the emergence and spread of human infectious diseases.
- Chapter 6 discusses the role of biodiversity in world food production—on land, in freshwater, and in the oceans.
- Chapter 7 provides for the policy-maker a preliminary list of suggested options to consider in addressing all of the above issues.

More than 60 scientists from around the world, each bringing an enormous wealth of experience and expertise, have joined me in compiling the material for this report. I cannot thank them enough for their creativity and wisdom and just plain hard work. All of us believe this report can help the public understand that human beings are an integral part of nature, and that our health depends ultimately on the health of its species and on the natural functioning of its ecosystems. All of us hope that our efforts will help guide policy-makers in developing innovative and equitable policies based on sound science that will effectively preserve biodiversity and promote human health for generations to come. And all of us share the conviction that once people recognize how much is at stake with their health and lives, and particularly with the health and lives of their children, they will do everything in their power to protect the global environment.

Eric Chivian M.D.
Director
Center for Health and the Global Environment
Harvard Medical School
chapter 3 Medicines from Natural Sources

Figure 1 Taxus brevifolia (Pacific Yew Tree).
History

Plants have formed the basis of traditional medicine systems that have been in existence for thousands of years. The first records are from Mesopotamia and date from about 2600 B.C.; among the substances used were oils of *Cedrus* species (cedar) and *Cupressus sempervirens* (cypress), *Glycyrrhiza glabra* (licorice), *Commiphora* species (myrrh), and *Papaver somniferum* (opium poppy), all of which are still in use today for the treatment of various ailments. Egyptian medicine dates from about 2900 B.C., with the best known Egyptian pharmacopeia being the Ebers Papyrus dating from 1500 B.C.; this describes some 700 drugs (mostly plants), and includes many formulas. The Chinese *Materia Medica* has been extensively documented over the centuries, with the first record containing 52 medicines (Wu Shi Er Bing Fang, 1100 B.C.), followed by 365 medicines (Shennong Herbal ~100 B.C.), and then 850 medicines (Tang Herbal, 659 A.D.). Similarly, documentation of the Indian Ayurvedic system dates from about 1000 B.C.; this system formed the basis for the primary text of Tibetan Medicine, Gyu-zhi (Four Tantras; translated ~8th century A.D.).

In the ancient Western world, the Greeks contributed substantially to the development of herbal drugs, with Theophrastus (~300 B.C.), Dioscorides (100 A.D.) and Galen (130–200 A.D.) being the major influences. Except for some recording of this knowledge by monasteries in Western Europe during the Dark and Middle Ages (fifth to twelfth centuries), it was the Arabs who were mainly responsible for preserving much of the Greco-Roman expertise, and for expanding it to include the use of their own resources, notably Chinese and Indian herbs unknown to the Greco-Roman world. The Persian physician philosopher Avicenna (980–1037 A.D.), contributed much to the sciences of pharmacy and medicine through works such as *Canon Medicinae*, which attempted to integrate the medical teachings of Hippocrates and Galen with the biological insights of Aristotle, and which served as a textbook for medical students for centuries.

Current Usage of Plant-derived Materials

Even in modern times, plant-based systems continue to play an essential role in health care. It has been estimated by the World Health Organization that approximately 80% of the world’s population from developing countries rely mainly on traditional medicines (mostly derived from plants) for their primary health care. The WHO has recently decided to begin cataloguing and evaluating the safety and efficacy of these remedies. Plant products also play an important role in the health care for the remaining 20% in developing countries, and for those in industrialized countries as well. For example, analysis of data on prescriptions dispensed from community pharmacies in the United States from 1959 to 1980 indicated that about 25% contained plant extracts or active principles derived from higher plants. And at least 119 chemical compounds, derived from 90 plant species, are important drugs currently in use in one or more countries. Of these 119, 74 % were discovered during attempts to isolate the active chemicals from plants used in traditional medicines. Such compounds are not only useful as drugs in their own right, but may be even more useful as leads to other molecules, though synthetic in nature, that are based upon the active natural products.

There are many examples of such plant-based drugs in current use, some which are given below:

**Quinine**
The isolation of the anti-malarial drug, quinine, from the bark of *Cinchona* species (e.g., *C. officinalis*), was reported in 1820 by Caventou and Pelletier. The bark had long been used by indigenous people of the Amazon region for the treatment of fevers, and was introduced into Europe (early 1600s) to treat malaria. Using the structure as a lead, chemists synthesized the anti-malarial drugs, chloroquine and mefloquine.

**Artemisinin**
Another plant used in the treatment of fevers—for more than 2000 years in traditional Chinese medicine—*Artemisia annua* (Quinhasou) yielded the agent artemisinin in 1985. Its more soluble derivatives, artemether and artether, are currently in use against strains of malaria increasingly resistant to the first line treatments—chloroquine and sulfadoxine-pyrimethamine—and are considered to be the most effective anti-malarial agents on the market today.

**Morphine**
This opiate, isolated in 1816 by Serturner from the opium poppy, *Papaver somniferum*, had been used as an analgesic for over 4000 years. By using the structure as a model, chemists subsequently developed a series of highly effective synthetic opiate analgesic agents.

**Paclitaxel (Taxol® Bristol-Myers Squibb)**
Probably the most significant drug discovered and developed through the U.S. National Cancer Institute’s Developmental Therapeutics and Clinical Trials Evaluation Programs is paclitaxel, isolated in 1969 as part of a broad plant screening program, from the bark
of the Pacific Yew tree (*Taxus brevifolia*) (Figure 1). In early clinical trials (1989), it was found to be effective for inducing remission in cases of advanced ovarian cancers (by a mechanism unlike that of other known chemotherapeutic agents), and since that time, it has shown significant therapeutic benefit for other advanced malignancies, including lung cancers, malignant melanomas, lymphomas, and metastatic breast cancers. It has also shown promise in preventing the smooth muscle cell proliferation that can block arteries opened by stents. As its natural source of supply could not be relied upon (the number and distribution of Pacific Yew trees was simply not known), paclitaxel and other taxoids have been produced by semi-synthetic conversions of a precursor compound found in renewable yew tree needles. The paclitaxel story illustrates the great importance of conserving natural resources, as this highly effective therapeutic agent was discovered only because of a random screening of 35,000 plant samples. It also demonstrates how highly complex bioactive molecules found in nature like paclitaxel (Figure 2) are unlikely to be discovered by combinatorial chemistry alone, but how, once they are discovered, they can serve as models for synthetic or semi-synthetic therapeutic agents that may be as, or even more, effective than the original natural product.

**Figure 2** Taxol® (Paclitaxel) molecule, demonstrating a highly complex, interlocking ring structure that would be nearly impossible to discover by synthetic means alone.

and in the West. There are numerous other examples where ethnomedical information may be of utility.

**Curare**
This is a generic term for a group of arrow poisons from South America. They were first described by explorers such as Sir Walter Raleigh, dating from the end of the 16th Century. However, it was another 200 years before von Humboldt conducted a systematic search for the botanical sources of curare. Some curares from eastern Amazonia are derived mostly from various species of plants from the genus *Strychnos.* But it is the extracts from the South American vine *Chondrodendron* that are the most common curares, and which, because of their observed ability as neuromuscular blocking agents, were successfully employed (in 1932) for the treatment of tetanus muscle spasms and other spastic disorders. Isolation of the most active agent from *C. tomentosum,* t-tubocurarine, led to a number of synthetic and semi-synthetic reversible paralyzing agents, which are very widely used in general surgery today to achieve deep muscle relaxation (especially important during abdominal and orthopedic operations) without using high doses of general anesthetics.

“jaborandi, ruda-do-monte”
This material is extracted from the leaves of *Pilocarpus jaborandi* and is known in the West as pilocarpine. Indians of northeast Brazil, including the Apinaye, have used it as a stimulant for lactation and as a diuretic. The active principle, pilocarpine, was first isolated in Brazil by Coutinho in 1875. Pilocarpine is currently used medically to stimulate salivation following head and neck radiation treatments or in Sjögren’s syndrome (which affects the salivary glands), and in the treatment of open-angle glaucoma.

**Microbially-derived Agents**
Although significant emphasis has been given to plant-derived agents in the general literature, from the perspective of biodiversity, the most diverse organisms on the planet are the microbes. It is estimated that less than 5% of all microbial flora has been investigated to date, but it is likely that the percentage is much lower than this figure, as the micro-organisms present in most environments have barely been studied. Ordinary seawater, for example, contains more than 1000 microbes of multiple species per cubic centimeter. Similarly, in one cubic centimeter of soil, more than 1000 different species of microbial flora have been found, with less than 5% of these able to be cultured using current techniques.
What is particularly exciting in recent years is the work by a number of marine natural product chemists and molecular biologists who have begun to examine the essentially unexplored marine microbial world as a source for novel structures and pharmacologic activity. The work of Fenical’s group, for example, on marine microbes associated with invertebrates and plants, as well as on those that are free-living, has provided a small glimpse of the vast potential that is present in the oceans for the development of new medicines, made even greater by modern techniques of gene manipulation.

The microbes were an unappreciated resource for medicines until the chemical identification of the antibiotics penicillin and streptomycin was made in the early 1940s. The discovery of antibiotics and their subsequent production in massive quantities has revolutionized the treatment of many infectious diseases. However, as microbes rapidly evolve to develop resistance to available anti-microbials, it is a constant race for scientists to find novel compounds that are effective.

There are many examples of antibiotics originally obtained from microbes that are in current use, some of which are given below:

**Penicillins and Cephalosporins (the β-lactam antibiotics)**
In 1928, Alexander Fleming noticed that a fungus, *Pencillum notatum*, that had contaminated one of his cultures of staphylococcus bacteria, killed the bacteria adjacent to it. A decade later, the systemic drug penicillin was developed, and over the next several years, it proved to be a remarkably effective antibiotic for millions of patients. In the late 1940s, however, initial reports of bacterial resistance due to destruction of the antibiotic by microbes surfaced. Another group of β-lactam antibiotics, first isolated from the fungus *Cephalosporium acremonium*, was developed and was found to overcome these early cases of resistance. With modification of the basic nucleus of the β-lactam structure, whilst still maintaining activity, medicinal chemists were able to synthesize over 40,000 active β-lactam-containing molecules, approximately 30 of which are currently in use today.

*The Aminoglycosides*
Stimulated by the discovery of penicillin, Waksman and his co-workers investigated a number of tropical soil bacteria, the actinomycetes, to determine if they too contained anti-microbial compounds. In 1944, they reported the discovery of streptomycin, isolated from the bacterium *Streptomyces griseus*, that was highly effective against the bacterium causing tuberculosis, *Mycobacterium tuberculosis*. With the advent of resistance in *M. tuberculosis* and in other microbes, and with the identification of bacterial resistance mechanisms by Davies and his colleagues in the early 1970s, many semi-synthetic variants of the natural compounds discovered by Waksman, the aminoglycosides, have been made. These agents are still widely used in infectious disease treatment.

---

**Figure 3 Natural Product Drug Discovery and Development in the United States (in developing and other developed countries, a similar model is used).**
The Tetracyclines
These were another discovery by the Waksman group, which systematically screened soil samples from many parts of the world to find antibiotic-producing micro-organisms. In conjunction with major pharmaceutical companies such as Lederle and Abbott, they isolated or synthesized many thousands of derivatives. The basic tetracyclines are still widely used as therapeutic agents, and currently, relatively simple derivatives of the original structures from 50 years ago, are in clinical trials as potential new therapies against resistant microbes.

The Anthracyclines
Rather than being used against microbes, these naturally-occurring agents, and the many thousands of their derivatives that have been synthesized and/or discovered over the last 40 years, are predominately directed against cancer cells. Perhaps the best known is Adriamycin, first reported in the late 1960s, which despite having significant side effects (irreversible cardiac toxicity), is still a prime treatment for breast and ovarian carcinomas.

Current Examples from Vertebrate and Invertebrate Sources
In addition to plants and microbes, there has been increasing attention paid to animals, both vertebrates and invertebrates, as sources for new medicines. One excellent example is the work initially conducted by Daly during the 1960s of the skin secretions of dendrobatid frogs from Ecuador, and of other “poison dart” frog species in Central and South America (see Chapter 4). This work has led to the identification of a number of alkaloid toxins that bind to multiple receptors in the membranes of nerve and muscle cells. One compound derived from these studies, which binds to nicotinic acid receptors associated with pain pathways, the synthetic ABT 594 (Abbott Laboratories), is in Phase II clinical trials, and has generated a great deal of interest, as it has been shown to be 30–100 times more potent as an analgesic than morphine.

Cone Snails
Each of the approximately 500 cone snail species is believed to produce its own distinct set of peptide toxins, numbering 100 on average, so there may be as many as 50,000 different toxins in all. Less than 0.2% of these have been characterized, and only a small subset of this number has been analyzed for biological activity. Despite these limited studies, several potential new medicines derived from conotoxins are being investigated:

- a pain killer called Prialt® (Elan Pharmaceuticals—formerly called Ziconotide) that is in extended Stage III clinical trials (Figure 3) and is reputed to be 1000 times more potent than morphine, but unlike morphine and other opiates, it does not lead to tolerance or addiction.
- a broad spectrum anti-epileptic agent that is in Stage I clinical trials for intractable epilepsy
- and drugs that may be used to prevent nerve cell death following strokes or head injuries, treat spasticity secondary to spinal cord injuries, and provide for the early diagnosis and treatment of small cell carcinomas of the lung, one of the most aggressive human cancers.

Cone snails may contain the largest and most clinically important pharmacopoeia of any genus in Nature.

Natural Pesticides
Most lay people usually think of natural products from only a drug, or “natural treatment,” perspective. However, a very important area that is not usually considered is the use of natural compounds as agricultural agents of many types, that keep people healthy by maintaining adequate food supplies and preventing malnutrition. These natural product agricultural agents, ranging from crude enriched extracts and their derivatives to purified compounds, are particularly important in developing countries, where the use of expensive synthetic agents is not possible. They are being used increasingly in developed countries as well, as organic farming methods proliferate.

Perhaps the most important use of such natural compounds is as insecticides. Insect pests are one of the major causes of poor agricultural yields, and the use of these natural insecticides can lower the costs of food production (or, for that matter, the production of
medicinal plants). Below are some important examples where traditional knowledge is being used in conjunction with modern chemistry.

**Pyrethroids**

One of the oldest and most successfully used plant products (from the 19th Century) is the powder from pyrethrum flowers, *Chrysanthemum cinerariaefolium*, originally native to the Dalmatian Mountains in Croatia (major producers currently are Kenya, Uganda, Rwanda, and Australia). Conventionally, the natural products from the pyrethrum flowers are referred to as pyrethrins; "pyrethroids" refer to insecticides that use pyrethrins as prototype structures. The pyrethroids act quickly on insects and do not concentrate in surface waters. All the decomposition products are of lower toxicity than the parent compound. Hence, there seems little risk that toxic residues will accumulate and contaminate the environment.

**Carbamate-based Insecticides**

Biologically active carbamates were used as far back as the 17th century in the old Calabar region of southeast Nigeria. The Efikis used to collect the beans from a plant later named *Physostigma venenosum* in order to subject prisoners to its toxic effects as a means of uncovering admissions of guilt. In 1925, the structure of the active agent, physostigmine, was determined, followed by its synthesis in 1935. Subsequently, a large number of similar compounds were synthesized and shown to inhibit the enzyme acetylcholinesterase, which is essential to the operation of muscles in all animals. These compounds cause rapid paralysis of insects, but frequently they are not lethal by themselves, so are often used in combination with other products.

**Neem**

Native to India and Burma, the neem tree is a member of the mahogany family *Meliaceae*, and is known as the margosa tree or Indian lilac, *Azadirachta indica* (Figure 4). A perennial, requiring little maintenance for growing, it has been introduced to West Africa and other parts of the world. Its insect control efficacy was first recognized by the fact that locusts would swarm on the *A. indica* tree but not feed. Extracts from the seeds and leaves have insect control activity and can be used without further refinement. Active ingredients have also been isolated and formulated as commercial products. In addition to its agricultural usage, Neem has been used medicinally for generations in India as a general antiseptic. No comprehensive toxicological data, however, is available.

![Figure 4 Neem tree (Azadirachta indica).](image)

**Nereistoxin-Related Insecticides**

The marine environment is also a source for insecticides. Nereistoxin is an insecticidal poison isolated from the marine worm, *Lumbrineris brevicirra*. Synthetic modification of neristoxin has led to a family of agents (cartap, bensultap, and thioiclom) that have been developed as commercial insecticides, and which are potent contact and stomach poisons for sucking and leaf-biting insects.

**Examples of Values of Natural Products as Pharmaceuticals**

A question that is often asked is whether there is any data on the financial value of natural product-derived drugs for pharmaceutical companies. A recent analysis by Newman and Laird (1999) demonstrated that the percentage of sales (not profits) derived from natural products or related compounds ranged from 50% for Merck to 8% for Johnson and Johnson, with the majority of companies falling between 15 and 30 percent. Companies were not included unless they had at least one drug that sold for more than US $1 billion. It should be emphasized that this was a one-time study using only 1997 sales figures for drugs that sold more than US $1 billion that year, and that almost all of the natural product-derived drugs in this analysis were microbial in origin. It was not for another two years that the first plant-derived drug to break sales figures of US $1 billion arrived, and that was Taxol®.
Suggested Readings


chapter 4 The Value of Plants, Animals, and Microbes to Medical Research

Figure 1 Polar bear mother and cubs, Canada.
Introduction

Biomedical research has long relied on other species—plants, animals, and microbes—to understand normal human physiology and to understand and treat human disease. From the bacteria E. coli, one five hundredth the thickness of a human hair, to an 11 foot tall, 1300 pound male polar bear; from the fruit fly Drosophila melanogaster, which has a life span of only days, to chimpanzees, which, like us, can live for decades, these and numerous other species have brought medicine into the modern era of antibiotics, anti-depressants, cancer therapy, organ transplantation, and open heart surgery (see Table 1).

Some species possess easy to study anatomical structures, like the giant axons of squid or the macroscopic eggs of the African frog Xenopus, that make them especially useful as laboratory subjects. Others like denning bears or the spiny dogfish shark Squalus acanthias have physiological processes so unique that they offer us clues, that might not otherwise be discovered, to the healthy functioning of the human body or to the treatment of human disease. Still others, because they are easy to keep in the laboratory, reproduce rapidly and in large numbers, and are able to produce genetically identical, unique strains have become the “workhorses” of animal experimentation. We owe an enormous debt to the countless mice, rats, guinea pigs, hamsters, rabbits, zebrafish, fruit flies, and other species that have been sacrificed to advance human health.

While evolution has resulted in significant differences between humans and other life forms, particularly when one looks at processes like higher brain functions or at behavior, nature has a striking uniformity at the molecular, cellular, tissue, organ, and organ system level that allows us to use a wide variety of other organisms to better understand ourselves. The reason for this uniformity becomes very clear when we look at our own genetic make-up. We share, for example, about 3000 genes out of our estimated 30,000 with both the fruit fly and the microscopic round worm Caenorhabditis elegans, the other two animals for which we know the full genome sequence. Even more surprisingly, we share 1000 genes with the unicellular yeast which has a nucleus, and 500 genes with bacteria which do not. This core of about 500 genes is universal to all living things and mediates such basic functions as DNA replication, the production of proteins from RNA, metabolism, electron transport, and the synthesis of the compound ATP, the energy currency for all life on this planet. The universality of these genes provides evidence that all extant organisms evolved from a common ancestor, which most likely had this core set of about 500 genes by 3 billion years ago.

For nearly every genome that has been sequenced, be it vertebrate or invertebrate animal or plant, about half of the DNA can be classified as shared amongst many species, inherited, and little changed from a common ancestor. The same holds true for the 300 or so genes known to be implicated in human disease. For example, among gene mutations that are linked to cancer, developmental abnormalities; diabetes; as well as to cardiovascular, endocrine, and immune system

<table>
<thead>
<tr>
<th>Table 1 Major Medical Developments Dependent on Animal Research.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local and general anesthetics</td>
</tr>
<tr>
<td>Use of insulin for diabetes</td>
</tr>
<tr>
<td>Penicillin and broad spectrum antibiotics</td>
</tr>
<tr>
<td>Polio, diphtheria, and whooping cough vaccines</td>
</tr>
<tr>
<td>Medications for high blood pressure</td>
</tr>
<tr>
<td>Heart and lung bypass machines for open heart surgery</td>
</tr>
<tr>
<td>Blood transfusion</td>
</tr>
<tr>
<td>Kidney dialysis</td>
</tr>
<tr>
<td>Transplantation of corneas, heart valves, hearts, kidneys,</td>
</tr>
<tr>
<td>and bone marrow</td>
</tr>
<tr>
<td>Effective painkillers</td>
</tr>
<tr>
<td>Anticoagulants</td>
</tr>
<tr>
<td>Asthma medications</td>
</tr>
<tr>
<td>Breast cancer treatments</td>
</tr>
<tr>
<td>Development of cardiac pacemakers</td>
</tr>
<tr>
<td>Leukemia treatments</td>
</tr>
<tr>
<td>CAT scans</td>
</tr>
<tr>
<td>Medications to treat depression</td>
</tr>
<tr>
<td>Drugs and tests for HIV AIDS</td>
</tr>
<tr>
<td>All medicine and vaccines used to treat animals by veterinarians</td>
</tr>
<tr>
<td>And all other human medicines (which are tested first on animals for toxicity)</td>
</tr>
</tbody>
</table>

The Value of Plants, Animals, and Microbes to Medical Research
A Brief History of Biomedical Research (see Figure 2)

Experimenting on animals in order to understand the structures and functions of the human body began in Western medicine, as far as it is documented, about 2500 years ago when Alcmaeon in Greece (~450 B.C.) cut the optic nerve in a living animal and noted that it became blind. Greek and Roman physicians continued such experimentation over the next several hundred years, culminating in Galen (129–199 A.D.), the great Greek physician to the Roman emperor Marcus Aurelius. He made many astute observations about human physiology by studying animals, but his enduring legacy was his treatise De Anatomicis Administrationibus (On Anatomical Procedures), in which he described for the first time precise scientific techniques for animal experimentation.

Following Galen, little progress was made in Western medicine (although there continued to be a flowering of medicine both in China and among Arab physicians) until the 16th and 17th centuries when some seminal discoveries were made from animal experimentation, including William Harvey’s determination of the human blood circulatory system in 1628. But it was not until the discovery of using ether for general anesthesia in the 1840s, the development of aseptic surgical techniques in the 1860s, and an understanding of the sciences of bacteriology and immunology in the late 19th Century that there was an explosion of animal experimentation.

Some of the historical milestones in medicine that have relied on experimentation with other species are noted in Figure 2, and some of the major discoveries in medicine that have depended on animal research are listed in Table 1. It should be mentioned that, in fact, all
medications, before being approved for use in humans, are tested for safety in animals (see Chapter 3, Figure 3). It should also be pointed out that veterinary medicine relies on animal research for the development of vaccinations, and for effective treatments for diseases and injuries in pets, domestic animals, and wildlife.

Although this chapter shall focus almost exclusively on biomedical research carried out on animals, it must be stated that plants and microbes have provided critically important insights as well, which modern medicine has long relied on. As an example, the Nobel Prize in Physiology or Medicine for 2001 recognized the discovery in baker’s yeast cells of a specific class of genes controlling the steps of cell division, work that has important implications for understanding and treating human cancers and other diseases.

**Concerns about the Use of Animals in Research**

While the use of animals is widely accepted as essential to biomedical research, there are some who believe that this practice should not be allowed under any circumstances. They argue that animals are sentient beings and that it is morally wrong to subject them to the pain and distress involved in experimental procedures or to the suffering related to housing them under unsuitable conditions. These arguments may at times be bolstered by examples that adequate alternatives to the use of animals in research sometimes exist—from epidemiological investigations, autopsy findings, careful clinical trials and observation, and human tissue and cell culture studies, or by occasional evidence that one cannot extrapolate from the findings in animals to human beings.

We do not intend to treat this highly important topic further in this chapter. Rather, we begin with the assumption that the use of animals, plants, and microorganisms in biomedical research is an ethical imperative, as it contributes immeasurably to reducing pain, suffering, and the loss of life in human beings, and is a critically important means for ensuring that humans are receiving safe and effective treatments. It goes without saying that all efforts should be made to ensure that research animals are treated humanely and with respect, and it needs to be acknowledged that animal welfare advocates have contributed significantly to focusing much-needed attention on this important issue.

**Genetics and the Use of Mice in Biomedical Research**

When researchers independently reported their re-discovery of Mendel’s Laws of Inheritance in 1900, each had worked with higher plants as their experimental material. The question immediately arose whether these laws applied to animals as well as plants, and the answer was not long in coming. By 1902 Cuénot in France had demonstrated Mendelian ratios for the inheritance of coat color characters in mice, and Bateson and Saunders had shown that the Mendelian laws applied to the inheritance of comb characteristics in chickens. Mouse genetics started on the course it was to follow for the next century in 1909 when two important events occurred. E. E. Tzyzer found that mice inherited resistance to the growth of transplanted tumors, and C. C. Little developed the first inbred mouse strain. It was in these efforts that the application of mouse genetics to the analysis of mammalian physiology, biochemistry, and pathology began.
Two themes dominated the first 50 years of mouse genetics. One was the study of genetic factors that determined susceptibility to transplanted tumors. The other was the effort to analyze the genetic basis for differences in the incidence of spontaneous tumors, eventually leading to the discovery of retroviruses and of their role in transforming normal cells to cancerous ones. These two lines of research provided the original motivation for establishing inbred mouse strains, which now number more than 300.

The period since 1980 has seen explosive advances in genetic technology, especially in our ability to engineer the genome, one gene at a time. In late 1980 and early 1981, six laboratories independently showed that rabbit DNA injected into mouse egg cells could become incorporated into chromosomes. The resulting offspring carried an entirely new gene, and this gene was functional. Thus it was shown that DNA from one group of mammals, rabbits, could function properly in another, mice, despite these species being separated by 75 million years of evolution.

In 1990 it became possible to replace an existing gene with an altered copy that had been rendered non-functional. This ability to “knockout” a gene function quickly led to a flood of experiments testing the function of specific genes in mammalian physiology, such as the role of p53, the most common gene altered in human tumors. At the present time, knockout mutations number in the thousands and have become a basic tool to understanding gene functions.

Among the hundreds of inbred mouse strains there are enormous differences in disease susceptibility, and it has been found that mice disease susceptibility genes, for example for developing hypertension, have their human counterparts. This concordance between mouse and man means that identifying disease causing genes in mice will be an important and efficient step, vastly reducing the cost and increasing the speed of identifying such genes in humans.

Our ability to find and identify genes participating in the common ills that afflict us will only increase. Mice get nearly all of the human ailments of public health concern, and the study of natural genetic variation among inbred mouse strains, combined with the ability to induce new mutations, will lead to a far more profound understanding of molecular pathology—how does disease come about at the cellular and molecular level and what are the critical molecular circuits and events?

Some Threatened Animals Important to Medical Research

Poison dart frogs

The family of frogs called the Dendrobatidae contains more than 80 species from the genera Phyllobates, Dendrobates, Epipedobates and Minyobates that live in lowland tropical rainforests of Central and South America. Although no frogs from this family are on the 2000 IUCN Red List of Threatened Animals, their ranges are often limited, and because of disease and rapidly expanding deforestation of rainforest habitats, some species must be considered to be at risk. These frogs are generally called “Poison Arrow” or “Poison Dart” frogs, but this name for the group as a whole is misleading, as only three species from western Colombia of the genus Phyllobates have been used by native Indians to poison arrows and blow gun darts. Many of the remaining species also contain toxic compounds, but at lower concentrations.

Of great interest is the remarkable diversity of biologically active alkaloids found in the skin secretions of these frogs, including the highly toxic batrachotoxins, isolated from a Colombian Phyllobates species. These alkaloids bind to voltage-dependent sodium channels at extremely low concentrations, locking the channels in the open position, thereby blocking nerve conduction and causing a sustained contraction in muscles. Because of this potent and selective binding ability, batrachotoxins have become central research tools in uncovering the structure and function of sodium channels in nerves and muscles. Without batrachotoxins, many fundamental insights about sodium channels, such as understanding their interactions with other toxins, and with drugs having local anesthetic, anti-arrhythmic, and anti-convulsant properties, would not have been possible.

The origin of the alkaloid toxins isolated from these frogs was a mystery, as alkaloids are plant compounds. By raising the frogs in captivity, it was found that they did not produce the toxins themselves. It is now believed that the frogs feed on ants or other arthropods that contain the alkaloids, which in turn obtain the alkaloids from certain plants. Despite the potency of these compounds, they might never have been discovered were it not for the ability of the frogs to bioaccumulate them at higher concentrations than are found elsewhere in the food chain. A search for alkaloid-containing arthropods may lead to the discovery of additional biologically active compounds of medical importance.
Cone Snails
Because they bind with such extreme selectivity to an enormous array of receptor sites, the toxins from cone snails have been widely used in biomedical research. For example, conotoxins have helped characterize some of the subtypes of nicotinic acetylcholine receptors in mammalian heart muscle, which has led to a better understanding of the mechanisms that control heart rate and contractility. They have also been used to study these receptor subtypes in skeletal muscle and brain. Other toxins have been employed in the identification of calcium, potassium, and sodium ion channel subtypes, greatly advancing our knowledge of these fundamental molecular units.

The enzyme gamma glutamyl-carboxylase, extracted from Cone snails (one of the only invertebrates that produce it), has been used to achieve a more complete understanding of the defective blood clotting cascade in patients with hemophilia B.

Conotoxins have also been used in research as immunoassays, as they can bind to some circulating antibodies that cause paraneoplastic syndromes. These are autoimmune neurological disorders seen in some types of cancer, where antibodies formed to bind to ion channel and other receptor antigens in cancer cell membranes, attack normal neurons and cause them to malfunction. By detecting the antibodies, conotoxins can provide an early diagnostic test for the cancer.

Bears
Nine bear species are listed on the 2000 IUCN Red List of Threatened Species, including the Polar Bear (*Ursus maritimus*), the Giant Panda (*Ailuropoda melanoleuca*), and the Asiatic Black Bear (*Ursus thibetanus*). Bears are at risk primarily because of destruction of their habitat, but also because of over-hunting, driven in part by the high prices their body parts, believed to have medicinal value, bring in “black markets” in parts of Asia. Bear gallbladders, for example, have been sold for the equivalent of eighteen times their weight in gold.

The denning bear is the only mammal that fasts for 150 days while maintaining a normal body temperature (~97°F). Unlike some rodent species, bears do not actually hibernate, a state characterized by a lack of arousal and a markedly reduced metabolic rate. While denning, the bear is alert and reactive, even though it does not eat, drink, urinate, or defecate. In spite of these privations, the bear not only survives denning, but even grows. Female bears, in addition, can give birth to as many as five cubs during denning and nurse them.

An understanding of the physiological wonders of denning bears has come largely from studies on North American black bears (*Ursus americanus*) over the past 25 years by Ralph Nelson and his colleagues. The bear accomplishes the seemingly impossible combination of fasting and growth by recycling all of its body wastes. Calcium lost from bone is recycled back into bone. The urine that is continually formed is recycled back into the blood stream through absorption by the bladder, and the main urinary waste, urea, is recycled back into amino acids and protein. Free fatty acids are recycled back into fat tissue, controlling blood levels of ketones. Body fat supplies both energy and metabolic water. Because of these processes, the lean body mass of denning bears increases, while body fat is lost.

**Osteoporosis**
Despite inactivity and a lack of weight bearing, bears do not lose bone mass, that is, they do not develop osteoporosis, during the five months or more of denning. Loss of bone mass is a phenomenon that occurs in all other mammalian species, including humans, with decreased mechanical use of the skeleton. A bed-ridden human patient, for example, loses one fourth to one third of his or her bone mass during a five month period. A research extract, isolated from the blood of denning bears by Nelson and his team, has been shown experimentally to significantly stimulate bone forming cells called osteoblasts and to inhibit osteoclasts, cells that dissolve bone. It also restored normal bone formation in rats that had their ovaries removed and had developed osteoporosis as a result. Osteoporosis is a major public health problem, particularly among the inactive elderly and in paralyzed and bed-ridden patients, that has largely defied treatment. In the U.S. alone, osteoporosis afflicts approximately 28 million people, a major proportion of which are post-menopausal women, causes 1.5 million bone fractures and 70,000 deaths each year, and costs the U.S. economy U.S. $13.8 billion annually. Insights derived from denning bears could lead to new treatments for this dreaded disease.

**Renal Failure**
Bears also do not urinate for a period lasting five months or more, but they are able to stay healthy, as they recycle urea to make new amino acids and proteins. Humans unable to excrete their urinary wastes die after several days. In human patients with chronic renal failure, lowering protein in their diets can help lower the production of urea in early stages, but in those who
progress to end-stage renal disease, their only treatment is kidney dialysis or a kidney transplant. The Nelson team’s research extract has been shown to stimulate the recycling of urea under experimental conditions in a non-hibernating, non-denning mammal, the guinea pig. Normally, humans can recycle about 25% of the urea they produce each day, but if, like the denning bear, they could recycle essentially all of it, they could possibly avoid the toxic and lethal effects of renal failure, a condition that costs the U.S. economy an additional U.S. $10 billion each year.

_Polar Bears (Figure 1)_

One would think that a species living at the northern fringe of the earth would be safe from the threat of human over-exploitation and human-caused habitat destruction. However, this is not the case for the polar bear (*Ursus maritimus*). In addition to over-hunting, and the loss of habitat (primarily the result of oil and gas exploration, and of development), polar bears face another threat. Increased temperatures from global warming (warming is greatest at the highest latitudes) have significantly thinned arctic ice, compromising the polar bear’s ability to hunt for seals, its primary food. Under normal conditions for the first few months of spring, polar bears consume large quantities of seal fat and little else. When summer arrives, they are obese, at which point they begin fasting for several months.

Free-ranging wild polar bears are typically insulin-resistant throughout the year, the condition that characterizes Type II diabetes mellitus. In addition, despite prolonged fasting during denning, they show no evidence of essential fatty acid deficiency, presumably because they are able to mobilize them from storage in body fat in the precise amounts necessary for metabolic processes. An understanding of the complexities of glucose and fat metabolism, and of the regulation of insulin in polar bears could lead to new insights about preventing and treating Type II diabetes mellitus, a disorder that is reaching epidemic proportions in the U.S. Similarly, uncovering the dynamics of essential fatty acid metabolism in polar bears could lead to a better understanding of a variety of human diseases associated with a deficiency or imbalance of these compounds, including chronic malnutrition, anorexia nervosa and atherosclerosis.

Denning bears may also provide clues for the prevention and treatment of other human conditions, including severe anxiety, obesity, and Type I diabetes mellitus.

**Non-human primates**

The use of non-human primates in basic and applied biomedical research has grown steadily in the last 100 years—in endocrinology, immunology, microbiology, toxicology, dermatology, ophthalmology, oncology, developmental biology, virology, drug metabolism, aging, and the neurosciences. For many diseases, there is no other medical model that can be used. At the same time, many primate species are endangered, including those species closest to us—gorillas and chimpanzees (the chimpanzee genome differs from that in humans by less then 1.5%). Many primates are threatened by loss of habitat secondary to deforestation and development; by infectious diseases, some caught from encroaching human populations; and by hunting, particularly for the “bushmeat trade.”

**Virology**

HIV/AIDS and hepatitis are among a number of human viral diseases that have been studied using primates.

**HIV/AIDS**

Several Asian macaque monkey species develop an AIDS-like disease following exposure to simian immunodeciency viruses (SIV), a family of viruses that share DNA sequences with human immunodeciency viruses. The similarity of the clinical presentation between Asian macaque AIDS and HIV/AIDS has led to their being used in vaccine development, and in understanding HIV/AIDS in humans, including such issues as maternal-fetal transmission. The chimpanzee is the only nonhuman species known to be susceptible to infection with the human immunodeciency virus, HIV-1. They have been used to determine the safety and efficacy of HIV/AIDS vaccines and medications.

There is growing evidence that the original source of the HIV-1 infection was a chimpanzee subspecies *Pan troglodytes troglodytes*, and that humans were infected by exposure to the blood of this animal on multiple occasions. Similarly the source of the HIV-2 infection has been traced to the sooty mangabey (*Cercocebus atys*). According to the WHO, more than 60 million people have been infected with HIV since the pandemic began, and there have been more than 21 million deaths. Destruction of habitat, and the slaughter of chimpanzees by the “bushmeat” trade will lead to the loss of those species in the wild that can help us more fully understand the genesis and dynamics of this disease, and find more effective preventive measures and treatments.
Hepatitis
Although the occurrence of jaundice was reported as early as the eighth century, it was not until after World War II that the viral cause of hepatitis was established. Two forms of the disease—hepatitis A and B were recognized. Today, at least five viruses that cause hepatitis in man have been identified: A and E are transmitted by the fecal-oral route and generally cause only acute, self-limited infections; while hepatitis B, C, and D viruses are transmitted by blood and other body fluids, with the possibility of persistence and the development of liver cirrhosis and primary hepatocellular carcinoma. Together, the hepatitis viruses represent a global health problem associated with high levels of morbidity and mortality. At present, some monkey and ape species are the only available animal models for the propagation of these viruses as well as for studies of their biology and pathogenesis. They have been indispensable in the development of vaccines, and are being used to understand why hepatitis E viral infections can cause a fulminant hepatitis in pregnant women in some developing countries, and high levels of mortality.

Hemolytic Disease in Newborn
The discovery of the Rh blood group factor in humans was made using red blood cells (RBC) from rhesus monkeys. From this discovery and other related work it became widely known that blood group incompatibility between mother and fetus could lead to hemolytic disease of the newborn (HDN) and fetal death. HDN, also known as “erythroblastosis fetalis”, occurs when a woman becomes immunized to antigens carried by fetal RBC. These antibodies cross the placenta, coat fetal RBC, and cause their destruction. To survive and prevent anemia, the fetus must generate new RBC rapidly enough to replace those being destroyed. HDN has been demonstrated to occur spontaneously in monkeys and apes (e.g. marmosets, baboons, chimpanzees, and orangutans) which have been employed to better understand the condition in humans.

Reproductive Cycles
It was in studying the rhesus monkey and other Old World Monkeys (Catarrhini) which have similar hormone patterns, that the human reproductive cycle began to be understood. Research is continuing to provide insights into fertility control and early pregnancy loss.

Suggested Readings
Research Defence Society Website
www.rds-online.org.uk/home.html