Biodiversity: Its Importance to Human Health

Interim Executive Summary

Editor
Eric Chivian M.D.

**A Project
of the Center
for Health
and the Global
Environment**

Harvard Medical School

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

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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 needing these resources more than ever, having increased 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 fresh water, 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, some 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 or more, 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), the United Nations Development Programme (UNDP), and the United Nations Environment Programme (UNEP), and to produce a report on the subject that would be the most comprehensive one available. Happily, the WHO, UNDP, 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 2004. Upon completion, the report will be presented to the WHO, UNDP, UNEP, to the U.N. Convention on Biological Diversity, and to other agencies and policy-making bodies, including the U.S. Congress.

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.
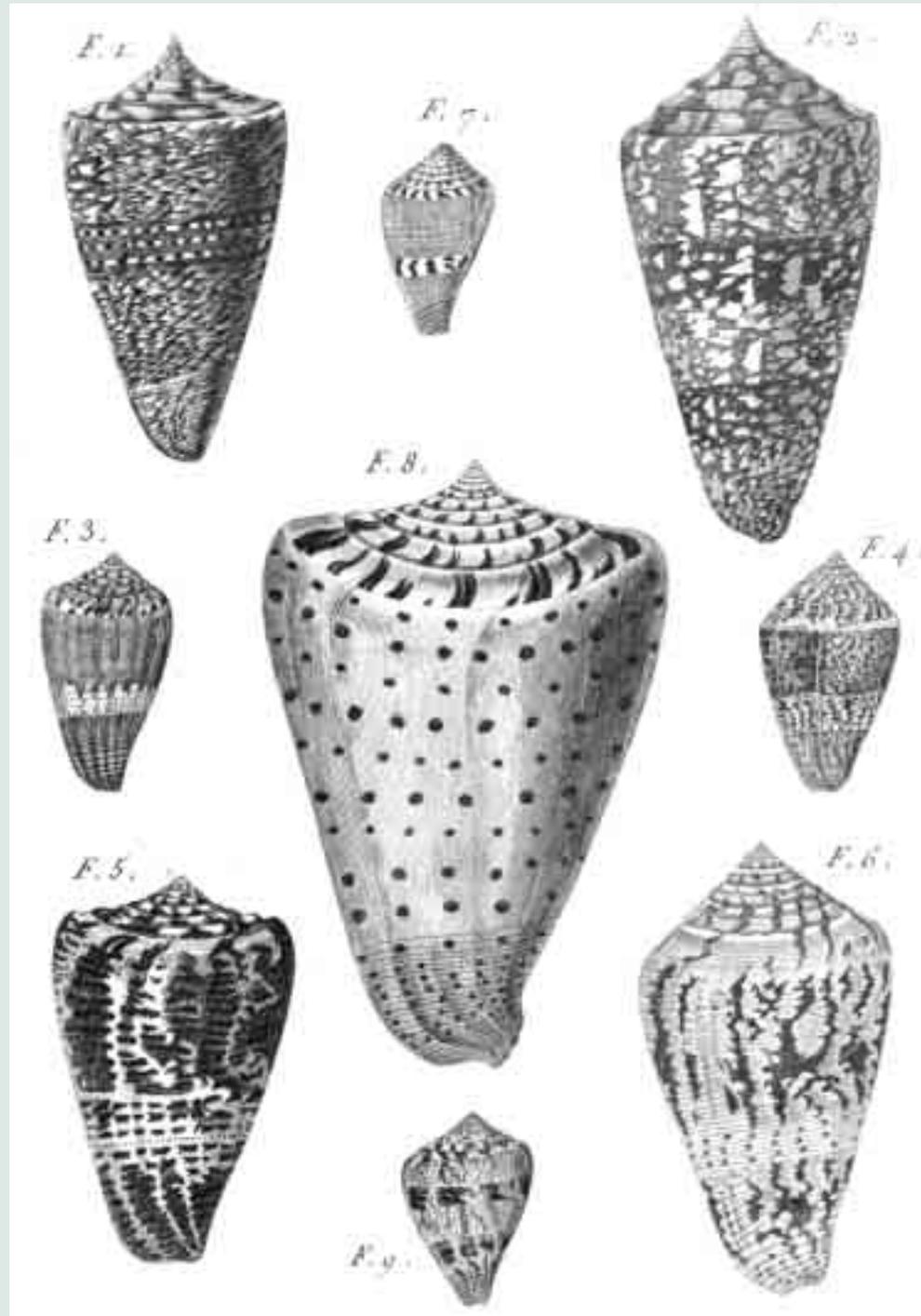
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chapter 1 **Biodiversity**

Figure 1 *Cone snail species.*

What Is Biodiversity?

Biodiversity is the variety of life—its ecosystems, species, populations, and genes. Human actions towards the land, freshwater, and oceans have already caused biodiversity to decline. Even greater losses will occur in the future if humanity continues its present unsustainable use of natural resources. In documenting this decline, there has been a focus on species extinctions, the most obvious manifestation of biodiverity loss. In addition, there is the loss of ecosystems, populations, and genes. All these are the only truly irreversible consequences of environmental change. When any of these is lost, it is gone forever. Species losses are also the aspect of biodiversity loss that is most often considered, for example, by the U.N. Convention on Biological Diversity. This chapter, too, will focus on species extinctions. The subject is broader and more complex than this, however. Even a species that survives can lose much of its genetic diversity if local populations are lost from most of its original range. Furthermore, ecosystems may shrink in area dramatically and lose many of their functions, even though their constituent species manage to survive. The loss of ecosystems, species, populations, and genes all have implications for human health.

The Rates of Natural and Present Day Species Extinction

Estimation of the absolute rates of species extinction: how many species are there?

Any *absolute* estimate of extinction rate, such as the number of extinctions per year, requires that we know how many species there are. We do not, and the problems of estimating their numbers are formidable. Taxonomists have described, that is, given names to, slightly more than one and a half million species **(see Table 1).** Only about 100,000 of these—terrestrial vertebrates, some flowering plants, and invertebrates with pretty shells or wings—are popular enough for taxonomists to know them well. Birds are exceptionally well-known, with roughly 10,000 species described, and only one or two new species named each year.

In some groups, we may have more names than the species they represent. Those who describe species cannot always be certain that the specimen in hand has not been given a name by someone else in a different country and (sometimes) in a different century. The more serious error, however, is that in all potentially species-rich groups, the estimates of numbers of species far exceed the number of named species. Moreover, taxonomists have only sparsely sampled some potentially rich communities, such as the deep oceans, the canopies of rainforests, and the microscopic world. Table 1 also provides estimates of how many species are likely to exist.

These estimates of species numbers exclude microbes, for there is no universally accepted definition of species for such organisms as bacteria and viruses. The genetic diversity of microbes is substantial: a pinch of soil may contain thousands of different types, and recent surveys of the human mouth have identified hundreds of different bacteria. How widespread are these types—for example, do all soils have the same or different varieties —is still a matter to be resolved.

What has limited our appreciation of the diversity of microbes has been their small size, the fact that they are often morphologically identical, and the fact that most microbes cannot be cultured. It was not until molecular sequencing (by looking at ribosomal RNA) that the size and complexity of the microbial world began to be uncovered. Today, many biologists accept that the tree of life, rather than being dominated by animal and plant kingdoms, is, instead, divided into three domains—Bacteria and Archaea (which lack a nucleus), and Eucarya (which have a nucleus)—all three domains are composed almost entirely of microbial organisms **(Figure 2)**. For the purposes of this chapter, we shall concentrate on the macroscopic world of plants, animals, and fungi, for that is what we know best.

If we exclude most of the microbial world in estimates of the total number of species, then we come up with a figure of between 7 and 15 million—say 10 million to the nearest factor of 10.

Table 1 *Number of Named Distinct Living Species and Estimated Total Number of Species.*

Group	Number Of Named Species (in thousands)	Estimated Total Number of Species (in thousands)
Protozoa	40	100
Algae	40	300
Plants	270	320
Fungi	70	500
Animals		
Vertebrates	45	50
Nematodes	15	500
Molluscs	70	120
Arthropods Total	855	4650
Crustaceans	40	150
Arachnids	75	500
Insects	720	4000
Other animals	95	250
Total	**1,500**	**6,800**

Figure 2 *Three Domains of Living Organisms (The phylogenetic tree based on small-subunit ribosomal RNA sequences. N.B. the position of the branches Coprinus—fungi, Homo—animals, and Zea—plants).*
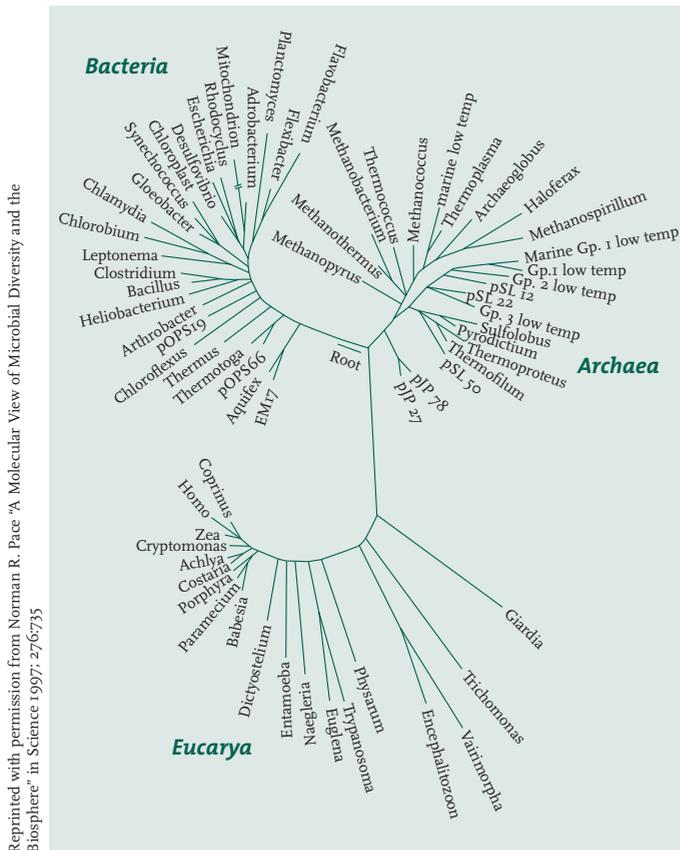
Relative rates of extinction: calculating background extinction rates

What is the background rate of extinction: that is, how fast did species disappear in the absence of human impacts? Various sources of information support the benchmark of a species lifetime at a million years or so, and the consequent background rate of extinction at no more than one species per million species per year.

Relative rates of extinction: Recent extinction rates

To what extent has our species increased extinction rates above background levels? If we are to use examples of species extinctions from certain groups that are well studied, it is necessary that they be representative. It is believed, with high statistical confidence, that those that have been used are indeed highly representative, being diverse in their natural histories and evolutionary origins. Extrapolating from these examples, one arrives at a current global rate of extinction that is at least several hundred times background rates **(see Table 2).**

Relative rates of extinction: predicting future rates of extinction from species currently threatened

For vertebrates, there are also world-wide surveys of the numbers of threatened species. *Threatened* has a specific meaning: it means that experts consider the species to have a high probability of extinction within the next few decades. For birds, 1,100 of the roughly 10,000 species known are considered to be threatened. Suppose that *all* these threatened species were to become extinct in the next 100 years (many would go sooner, of course). If so, then future rates of extinction for birds would be 1,100 extinctions per million species per year, or more than one thousand times background rates **(Table 2)**.

There are many factors that can threaten species survival that we cannot easily anticipate. For example, accidentally or deliberately introduced species may be the cause of many species extinctions.

While predicting future extinctions from introduced species or from other factors such as global climate change may not be possible, it may be possible to predict the magnitude of extinctions from habitat destruction, the factor usually cited as being the most important cause of extinctions (for birds, it is implicated in ~75% of the 1,100 threatened species). Habitat destruction is continuing and, in some cases, accelerating, so that some now-common species may lose their habitat within decades.

The loss of populations and genes

While much of the concern over the loss of biodiversity centers on the *global* loss of species, most of the benefits biodiversity confers depend on *local* species populations. An obvious example is a forest that provides protection to a city's watershed. While no species might become extinct globally if the forest were to be cut down, there would be a loss of the ecosystem services the forest provided—e.g. in preventing soil erosion and filtering out pollutants in ground water. Simply, it is the *local* loss of diversity that is important in this case. In addition, populations also supply genetic diversity, since different populations across a species' range will differ to varying degrees in their genetic composition. Such genetic diversity has a value for agricultural crops, for example, where plant breeders may rely on the diversity of genes in the wild relatives of those crops as a source of genes that confer resistance to disease. Thus, as populations are eliminated locally, genes may become extinct globally.

An average species consists of 220 populations, suggesting that there may be more than 2 billion populations globally, of which, it is estimated, 160 million populations (8%) are lost each decade. If present trends

continue, while many species may be saved in protected areas (such as national parks and zoos), those species will be just remnants of their once geographically extensive and genetically diverse selves.

The loss of ecosystems

While conservation justifiably prioritizes tropical moist forests because they are thought to hold such a large fraction of the world's species, a comprehensive strategy should also save distinctive ecosystems, not only because of the services that they provide, but because of the characteristic species they contain. Tropical dry forests, tundra, temperate grasslands, lakes, polar seas, and mangroves are all examples. Importantly, these biological communities house distinctive ecological and evolutionary phenomena. Some of these major habitat types, such as tropical dry forests and Mediterranean-climate shrublands are, on average, even more threatened than are tropical moist forests and require immediate conservation action. The Everglades of Florida or Brazil's Pantanal, for example, do not rank as places with a high concentration of species, but achieve prominence because flooded grasslands are globally scarce and uniformly vulnerable. Other regions attain prominence because of the biological phenomena they house, such as the Arctic tundra and its migratory shorebirds, polar bears, and caribou.

The Factors Causing Extinction

Habitat loss: On land

Habitat loss is widely believed to be the predominant cause of extinction. There are parts of the world, such as Europe and eastern North America, however, where human actions have extensively modified terrestrial habitats, yet these areas are not extinction centers. Clearly, habitat destruction causes different numbers of extinctions in different places.

What are the features common to centers of human-caused extinctions? For one, each area holds a high proportion of species found nowhere else.

Scientists call such species endemics. Remote islands are rich in *endemics*. Endemics constitute 90% of Hawaiian plants, 100% of Hawaiian land birds. There are continental areas that are rich in endemics, too. About 70% of the plants in the southern part of South Africa, 74% of Australian mammals, over 90% of North American fish and the great majority of that continent's freshwater molluscs are endemic to those regions. In contrast, only ~1% of Britain's birds and plants are endemics.

Past extinctions are so concentrated in small, endemic-rich areas that the analysis of global extinction is effectively the study of extinctions in one or a few extinction centers. Why should this be?

Consider some simple models of extinction. The simplest supposes only that some species groups are more vulnerable than others. This model does a poor job of predicting global patterns. First, the model predicts that the more species present, the more there will be to lose. Yet the number of species an area houses is not a good predictor of the number of extinctions. Relative to continents, islands house few species yet suffer many extinctions. Second, if island birds were intrinsically vulnerable to extinction, then Hawai'i and Britain with roughly the same number of breeding land birds, and both with widespread habitat modification, would have suffered equally. Hawai'i had more than 100 extinctions, Britain only three.

All the Hawaiian species were restricted to the islands; none of the British species were. This suggests another model of extinction. Imagine a "cookie-cutter" model where some cause destroys ("cuts out") a randomly selected area. Species also found elsewhere survive, for they can re-colonize. Only some of the endemics go extinct, the proportion depending on the extent of the destruction (see below). In this model, the number of extinctions correlates weakly with the area's total number of species, but strongly with the number of its endemics. By chance alone, small endemic-rich areas will contribute disproportionately to the total number of extinctions.

Table 2 *Past and Estimated Future Extinction Rates.*

Animal Group	Number of Species	Number of Past Extinctions	Time (years)	Past Number of Extinctions Per Million Species Per Year	Estimated Number of Future Extinctions	Time (years)	Estimated Future Number of Extinctions Per Million Species Per Year
Birds	9600	75	200	39	1100	100	1146
Mammals	4300	60	200	70	650	100	1512
Reptiles	4700	20	200	21	210	100	447
Frogs and toads	4000	5	25	50	89	100	223
Fresh water clams	1082	21	100	194	120	100	1109

Figure 3 *Extensive deforestation in the Amazon, Rondonia, Brazil, 2001. Landsat photo Courtesy of U.S. Geological Survey.*

This model is consistent with known mechanisms of extinction. Habitat destruction "cuts out" areas as the model implies. (Introduced species and other factors may also destroy species regionally.) This entirely self-evident model emphasizes the localization of endemics as the key variable in understanding global patterns of recent—and future—extinctions.

Species with small ranges are geographically concentrated. Scientists call these areas *centers of endemism*. Most of these areas are where threatened and recently extinct species are concentrated.

Hotspots: they are the combination of centers of endemism and unusual levels of habitat destruction. Only about 12% of the original habitat of these areas survives in the year 2000. Currently, hotspots make up only 1.4% of the Earth's total land surface, yet they contain more than one third of all known mammals, birds, reptiles, and amphibians. Of the surviving "hotspot" habitat, only about 37% is protected in any way. Sixteen of the 25 areas are forests and most of them are tropical forests. Even in the three that are relatively undisturbed—in the Amazon, the Congo, and New Guinea—only about half the original tropical forest remains **(see Figure 3)**. As a consequence of these high levels of habitat loss, these 25 hotspots are where the majority of threatened and recently extinct species are to be found.

Habitat loss: In the oceans

The seas cover more than two-thirds of the planet's surface, yet despite their extent, taxonomists have named only 250,000 to 300,000 marine species, compared to more than one million on land. Their count of marine species may be even more of an underestimate than it is for land, however, as the oceans are still very poorly explored, particularly microbially and at great depth. As on land, the peak of marine biodiversity lies in the tropics. Coral reefs account for almost 100,000 of marine species, yet their combined area is just 0.2% of the ocean surface. There are between four to five thousand species of fish on coral reefs, about 40% of the world's known marine fishes.

The global center of marine biodiversity lies in the South-East Asian archipelago, encompassing the Philippine and Indonesian islands. In the Atlantic Ocean, the highest levels of biodiversity are in the Caribbean.

An estimated 26% of the planet's reefs have been seriously damaged or destroyed by a combination of human activities—coastal development, over-fishing, land and marine based pollution, and global climate change. The reefs of South-East Asia and the Caribbean are the most threatened.

Cone Snails—Extremely Valuable to Medicine and Under Threat

Cone snails, a large genus of approximately 500 species (see Figure 1), inhabit shallow waters in tropical coral reefs and associated soft bottom habitats such as mangroves, seagrass beds, and mud flats. They defend themselves and paralyze their prey—worms, fish, and other molluscs—by injecting a cocktail of toxic peptides through a hollow, harpoon-like appendage. South-East Asia is home for 56% of the world's cone snail species, with the Philippines being an especially rich zone (8 species are found only in the Philippines). A new report estimates that 88% of the coral reefs in South-East Asia are threatened by human activities; in the Philippines, the figure is 97%. Threats to cone snails come from destruction of the reefs and of their other habitats (e.g. 50% of the world's mangroves have been cleared for wood and for development and aquaculture—in the Philippines, 60% have been cleared), and from direct exploitation, as cone snails are widely gathered for collectors and, recently, for biomedical research. Those species with highly restricted geographic ranges are the most at risk.

Habitat loss: Freshwater

Freshwater ecosystems are divided into two major classes—flowing (such as rivers and streams) and static (such as lakes and ponds). While the distribution of species is not as well known as for marine and terrestrial ecosystems, it is still clear that freshwater species are similarly concentrated. For fish, the major tropical rivers, such as the Amazon and its tributaries, hold a large fraction of the freshwater fish species on Earth. Tropical lakes, particularly those in the Rift Valley of East Africa, also have large numbers of endemic species. Some freshwater species are found in greatest numbers in temperate zones—for example, the greatest diversity of crayfishes, freshwater turtles, and molluscs is found in the United States.

Riverine habitats have been extensively modified by damming and by channelization—the process of straightening rivers and forcing them to flow along pre-determined channels (as opposed to their natural meanderings). These processes have threatened many of the species that live in these habitats, as has pollution caused by the run-off of toxic substances and of nutrients from sewage and fertilizers. Some lake species, especially those in boreal regions, may be at particular risk from the synergistic effects of climate warming, acid precipitation, and increased levels of ultraviolet radiation.

Pollution

Pollution is a special case of habitat destruction—chemical destruction rather than the more obvious physical destruction. Pollution occurs in all habitats—land, sea, and freshwater—and in the atmosphere. A growing body of evidence has implicated some synthetic organic pollutants with developmental abnormalities, and with effects on the endocrine, reproductive, neurologic, and immunologic systems of wildlife that may threaten their survival.

Introduced species

The problems of introduced species may be accelerating. After habitat loss, invasive species are thought to be the leading current cause of species extinctions. Faster and more extensive international travel makes accidental introductions more likely. Some introductions are deliberate. These include potential introductions that are radically new, such as genetically engineered organisms, be they microbes, plants, insects, or fish.

Not all species devastate the communities they enter. Some do, however, and the example of the accidentally introduced snake *Boiga irregularis* on Guam illustrates just how damaging an invasive species can be. *Boiga* drove seven endemic species of birds to

extinction on Guam. Were this snake to successfully colonize Hawaiʻi, (some individuals have arrived but are thought not to have lived long), then all of its birds could be at risk.

Over-harvesting

Humans harvest some species to very low numbers and drive others to extinction. Over-harvesting by hunting, fishing, or collecting means that species are driven to such low levels that the exploitation is not sustainable. While the most famous examples involve marine resources—whales and fisheries—plants (especially those valued for medicines) and higher primates, hunted for "bushmeat," can be exterminated in this way.

Secondary extinctions

Once one species goes extinct, there will likely be many other extinctions as a consequence. Some are simple to understand: for every bird or mammal or insect that goes extinct, there will likely be a number of parasite species or bacteria that will also disappear, as they are host specific—unable to live on any other host.

Other changes can be quite complicated. Species are bound together in ecological communities to form a food web of species interactions. Once a species is lost, the species that fed upon, were fed upon, benefited, or competed with that species will also be affected. These species in turn may affect yet other species. Ecological theory suggests that the patterns of secondary extinctions may be quite complicated and thus difficult to demonstrate or predict.

Global climate change

The global climate has warmed over the last century by about 0.6 degrees C., and animals and plants have responded in many ways as a consequence. Plants leaf out or flower earlier, migratory birds arrive earlier in the spring, and species ranges move towards the poles or to higher altitudes. Some ecosystems such as alpine meadows, cloud forests, arctic tundra, and coral reefs are especially sensitive to warming, and species in these regions may be particularly at risk.

While many species have demonstrated changes in the timing of life stages and in their ranges that could affect survival, it is not certain whether global climate change has caused any extinctions to date. Two possible examples are the golden toad and the harlequin frog from Costa Rica's Monteverde Cloud Forest Reserve, whose disappearances seem strongly linked to unusually warm and dry weather caused by the powerful El Niño event of 1996 and 1997. There is growing evidence, although not conclusive, that global warming has played a role in the increased strength and duration of El Niño events over the past decade. Mean global

surface temperatures are expected to increase by 1.4 to 5.8 degrees C. (2.5 to 10.4 degrees F.) by the year 2100. The magnitude and the rate of this increase, unprecedented for the last 10,000 years, will threaten the survival of many species, especially those unable to migrate to new ranges or otherwise adapt. Global climate change, by itself or acting synergistically with other environmental changes secondary to human activity, could well become the factor most responsible for species extinctions over the next 100 years.

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chapter 2 **Ecosystem Services**

Figure 1

Hand-Pollination of Apple Blossoms in Nepal—Bees in Maoxian County, at the border between China and Nepal, have gone extinct, forcing people to pollinate apple trees by hand.
It takes 20–25 people to pollinate 100 trees, a task that can be performed by 2 bee colonies.

What Are Ecosystem Services?

An ecosystem is an array of living things (plants, animals, and microbes) and the physical and chemical environment with which they interact. Examples of ecosystems include forests, wetlands, grasslands, streams, and estuaries. Healthy ecosystems provide the conditions and processes that sustain human life. In addition to providing goods such as foods and medicines, ecosystems also provide us with services, such as purification of air and water, the binding of toxins, decomposition of wastes, mitigation of floods, moderation of storm surges, stabilization of landscapes, and regulation of climate. We tend to take these services for granted and do not generally recognize that we cannot live without them, nor can other life on this planet.

What Is the Value of These Services?

Healthy ecosystems deliver life-sustaining services for free, and in many cases on a scale so large and complex that humanity would find it practically impossible to substitute for them. With respect to complexity, we often do not know which species are necessary for the services to work, what numbers they must be present in, and whether there are "keystone" species for ecosystem services. Disruption of these natural services can have catastrophic effects. For example, if natural pest control services ceased or populations of bees and other pollinators crashed, there could be major crop failures **(see Figure 1).** If the carbon cycle were badly disrupted, rapid climate change could threaten whole societies. From an economic standpoint, numerous examples illustrate that ecosystem services that have been diminished by human activities can be restored for a fraction of the cost of building artificial substitutes.

New York City's water quality was deteriorating due to development in the Catskill Mountains where the city's water supply originates. The cost of a filtration plant to deal with the increasing sewage and agricultural runoff would have been U.S. $5–8 billion plus an annual operating cost of U.S. $300–$500 million. Alternatively, a one-time expenditure of U.S. $1.5 billion was able to restore the integrity of the watershed's natural purification services by purchasing and halting development on land in the Catskills, compensating landowners for restrictions on private development, and subsidizing improvement of septic systems.

Examples of Ecosystem Services

Cycling and filtration processes

1. Air Purification

Forest canopies function as particulate filters and chemical reaction sites that help regulate the composition of the atmosphere and purify our air. Particulates resulting from the combustion of coal and oil, cement production, lime kiln operation, incineration, and agricultural activities are captured by forest canopies. Moist leaf surfaces also provide sites on which potentially polluting compounds can be transformed into harmless ones **(see Figure 2).**

Microbes in well-drained soils of tropical forests can produce large quantities of nitric oxide. Nitric oxide is a very reactive gas, which, as it moves through the forest canopy, combines with other chemicals on leaf surfaces. In combined form it does not reach the air above the canopy, where it otherwise would have catalyzed photochemical reactions in the atmosphere leading to the production of tropospheric ozone. Tropospheric ozone is a greenhouse gas and is also a pollutant that adversely affects both plants and animals, including humans.

2. Watershed Services

Forests regulate water flows to downstream areas, yielding relatively regular and predictable flows. Deforestation often leads to disruption of the natural flow pattern, causing cycles of flood and drought. Forests, especially forest soils, also act like massive filters, purifying water as it drips through the forest ecosystem **(Figure 2).**

In a healthy, middle-aged forest in New England, rain falling enters with a nitrogen load of about 8 pounds per acre each year. Stream water leaving this forest will often contain less than one-tenth of the nitrogen entering in rainfall.

3. Purification of Fresh Waters

Wetlands absorb and recycle nutrients from human settlements. As water flows through wetlands, plant, microbe, and sediment processes strip out nutrients such as nitrogen and phosphorus. Plants take up these nutrients and incorporate them into root, stem, and leaf material. Some microbes transform a water-soluble form of nitrogen into gaseous forms of nitrogen. Constructed wetlands are designed to use the nutrient retention and processing features of natural wetlands to remove nutrients and toxins from water.

Nitrogen pollution became a serious problem in the waters around Stockholm, Sweden. Restoring wetlands to reduce nitrogen loading was considerably less expensive than the construction of wastewater treatment plants. Besides the nitrogen filtering, the restored wetlands of the archipelago

around Stockholm supply a number of ancillary benefits including habitat for rare plants and animals and recreational opportunities.

4. Maintaining Water Quality in Estuaries

In many parts of the world, rivers carry excessive nutrients from runoff to coastal estuaries. The resulting nutrient over-enrichment (eutrophication) causes low dissolved oxygen levels, harmful algal blooms, and loss of submerged aquatic vegetation. Bivalve molluscs including mussels, clams, and oysters act as filtering systems for estuaries that remove suspended materials and consume algae, addressing the overproduction problem.

For centuries, the oyster population of the Chesapeake Bay was capable of filtering a volume of water equal to the complete volume of the Bay in a three-day period. Pollution, habitat destruction, over-harvesting, and other pressures have dramatically reduced the oyster population, greatly diminishing this critical filtering service. With the diminished oyster population the filtering now takes a year, and the waters of the Bay are poorer in oxygen and generally more polluted.

5. Binding Toxic Substances

Human activities have concentrated heavy metals, radioactive elements, and other toxins in various places, rendering some locations unusable and dangerous. In cleaning up such contaminated sites, we can utilize the capacity of some vascular plants to concentrate toxic substances without harming themselves. For example, mustard plants accumulate lead and certain ferns sop up arsenic.

In a small pond near the Chernobyl nuclear power plant that was contaminated with Strontium-90, Cesium-137, and other harmful radioactive substances released during the reactor fire in 1986, scientists grew sunflowers on small styrofoam rafts. With the roots of the sunflowers dangling in the water, the sunflowers rapidly accumulated levels of radioactive cesium and strontium that were several thousand times higher than the concentrations in the water.

6. Detoxification of Sediments and Soils

Microbes can help detoxify some human-generated wastes. For example, oil spilled into estuaries and marine ecosystems poses health risks to humans and other species. When certain compounds from petroleum hydrocarbons adhere to sinking particles, they settle to the sediment surface, where naturally occurring microbes can detoxify the compounds and ultimately degrade them to carbon dioxide and water.

7. Maintenance of Soil Fertility

Soils, with their active microbial and animal populations, have the capacity to supply adequate nutrients to plants in suitable proportions. Soil animals and microbes break down organic matter and release nutrients into the soil solution. Electrical charges carried by tiny soil particles give them the ability to retain these nutrients and release them to plant roots.

Stabilization processes

8. Control of potential pest and disease-causing species

Many weeds, insects, rodents, bacteria, fungi, and other pests compete with humans for food, affect fiber

Figure 2 *Forest Ecosystem Services.*

Forest canopy and leaf litter protect the soil surface from the erosive power of rain

Forest canopy purifies air by filtering particulates and providing chemical reaction sites where pollutants are detoxified

Forests help maintain the water cycle and stabilize local climates

Forest trees and plants store carbon and help slow human-caused global climate change

Forests provide critical habitat for plants, animals, and microbes

Forests provide goods such as food, timber, and medicines

Forest tree roots bind soils and help prevent erosion

Forest soils purify water, acting as a massive filter

Deep forest soils store large volumes of water

production, or spread disease. Certain animals and microbes do us the service of naturally controlling some of these pests, which can cause disease in plants and animals, including humans. In addition, using these natural controls as a model, scientists have developed some biological controls to replace pesticides.

In the 1950s, Chinese officials became concerned that birds were allegedly devouring large amounts of grain, and they declared small perching birds to be the enemy. Millions of Chinese began killing birds with frightening success; over several days in 1958, an estimated 800,000 birds were killed in Beijing alone. Major pest outbreaks resulted from this bird eradication program, leading to significant crop losses. The mistake was ultimately realized and the bird killing halted.

9. Mitigation of Floods

Floodplains are ecosystems that border rivers subject to flooding. Following excessive rains, flood waters flow over riverbanks and into these floodplain forests and wetlands. Some of the water is soaked up by the soil. When the floodwaters recede, they leave behind nutrient-rich sediments that enhance soil fertility, making these ecosystems extremely productive. Unaltered flood plains also provide habitat for many plant and animal species.

Because the flood mitigation services of the Mississippi River floodplain were not adequately recognized, nine U.S. midwestern states suffered a terrible toll in the floods of 1993: 50 people were killed, 70,000 lost their homes, and property losses were estimated at U.S. $12 billion. The high cost of the flood damage resulted, in part, from drainage of floodplain wetlands, building of permanent structures on the floodplain, and construction of levees.

10. Stabilization of Landscapes against Erosion

Forests and grasslands provide natural protection for soils against erosion in several ways. Plant canopies intercept rainfall and reduce the force with which rainwater hits the soil surface. Roots bind soil particles in place and prevent them from washing down slopes. And old root channels help to minimize the powerful force of surface runoff by routing water into the soil profile. Human actions, like clearing forests and plowing up grasslands to expand agriculture, accelerate erosion, causing the loss of useable cropland and other destructive outcomes.

Hurricane Mitch stalled off the coast of Honduras in October 1998, dropping up to 25 inches of rain in one six-hour period in some places. The resulting flooding and mud-slides killed over 10,000 people. Many of the deadly mud-slides occurred in areas where forests had been cleared for agriculture (Figure 3).

11. Buffering the Land against Ocean Storms

Salt marshes, mangrove forests, and other ecosystems buffer the coastline against ocean storms. Plants in these ecosystems stabilize submerged soil (sediment), thereby preventing coastal erosion. These ecosystems are also breeding grounds and nurseries for commercially important fish, and vital habitat for many bird and other species. Unfortunately, these ecosystems are being rapidly destroyed, filled in, and built upon.

Scientists at the Mangrove Ecosystems Research Centre in Hanoi, North Vietnam have found that mangroves are more effective than concrete sea walls in controlling raging floodwaters from tropical storms. Unfortunately, mangrove forests are under assault from coastal development, shrimp aquaculture, and unsustainable logging. Some countries, such as the Philippines, Bangladesh, and Guinea-Bissau have lost 70 percent or more of their mangrove swamps.

12. Carbon Sequestration on Land and Global Climate

Land ecosystems are large storehouses of carbon, both in plant tissue and in soil organic matter. By absorbing carbon, these ecosystems help slow the growth of atmospheric carbon dioxide. Were it not for this terrestrial carbon sink, the rate of carbon dioxide accumulation in the atmosphere would be almost twice as fast as it is today, leading to more rapid climate change.

Biodiversity preservation

13. Providing Critical Habitat

Ecosystems provide critical habitat for plant, animal, and microbial species that have intrinsic value, as well as providing valuable services to humans.

14. Genetic Library Function

The vast pool of novel genetic information stored in natural ecosystems represents the possibility of solutions to an enormous range of challenges. Genetic diversity is a rich, relatively untapped resource for present and future benefits in agriculture and medicine. Thirteen of the 20 best-selling prescription drugs in the U.S. are either natural products, natural products that have been slightly modified chemically, or manufactured drugs that were originally obtained from organisms.

Translocation processes

15. Pollination of Crops and Natural Vegetation

Many flowering plants rely on animals to help them mate by ensuring fertilization. Bees, butterflies, beetles, hummingbirds, bats, and other animals transport pollen, the male reproductive structures, from one plant to another, with enormous benefits to humanity (see Figure 1). Approximately one third of the world's food

Figure 3 *Severe Erosion from Hurricane Mitch—Miramondo Road, Honduras. The combination of deforestation and torrential rains from Hurricane Mitch at the end of October and early November, 1998 contributed to massive landslides in Honduras, destroying innumerable roads, 33,000 homes and 95 bridges, and resulting in 7000 deaths, 5000 missing, and tens of thousands of cases of cholera, malaria, and dengue fever.*

crops depends on these natural pollinators. In the U.S., honeybees pollinate about U.S. $10 billion worth of crops.

The oil palm was introduced into Malaysia from the forests of Cameroon in West Africa in 1917, but the weevil that pollinates the African oil palm was not introduced at the same time. For decades, the palm growers of Malaysia relied upon expensive, labor-intensive hand pollination. In 1980, the weevil was imported to Malaysia, boosting fruit yield in the palms 40–60 percent, and generating savings in labor cost of U.S. $140 million per year.

16. Dispersal of Seeds
Animals such as toucans, monkeys and fruit bats consume tree fruits and scatter piles of seed-rich dung across the landscape. Similarly, gray squirrels distribute acorns over broad areas propagating the spread of oak trees. This service helps trees populate their habitat, and migrate across the land in response to a variety of disturbances, including climate change.

Life-fulfilling functions

17. Recreation
Human health and well being are greatly enhanced by outdoor activities including hiking, skiing, camping, swimming, bird watching, bicycling, fishing, boating, and more. Ecosystems provide us with the natural environment in which to enjoy such activities.

18. Aesthetics
The natural world is a thing of beauty largely because of the diversity of life in its ecosystems. Being in Nature gives us comfort and hope. Nature inspires painters, writers, architects, and musicians to create works reflecting and celebrating its beauty. There is gathering evidence that our emotional well-being is enhanced by being in Nature.

Factors Affecting Ecosystem Services

Climate change
Human activities (such as burning fossil fuels) are increasing atmospheric concentrations of carbon dioxide and other gases, intensifying Earth's natural greenhouse effect. Global average surface temperature rose 0.6° C (1.0° F) during the 20th century and is projected to rise another 1.4 to 5.8° C (2.5 to 10.4° F) in the 21st century, mostly due to human activities. This temperature rise is associated with more extreme precipitation and faster evaporation of water, leading to greater frequency of both very wet and very dry conditions. Global sea level is rising, as water expands while warming, and as mountain glaciers around the world melt.

Many ecosystems will be highly vulnerable to the projected rate and magnitude of climate change. Some, including alpine meadows, mangrove forests, and coral reefs are likely to disappear entirely in some places. Other ecosystems are projected to become fragmented or experience major species shifts. The services lost through the disappearance or fragmentation of certain ecosystems will be costly or impossible to replace.

Deforestation
Temporary or permanent clearing of forests for agriculture or other uses is of major concern, particularly in the tropics. Forest destruction threatens the survival of native peoples. It results in decreased soil fertility and increased erosion. Uncontrolled soil erosion can affect the production of hydroelectric power as silt builds up behind dams. Increased sedimentation of waterways can harm downstream fisheries, and in coastal regions can result in the death of coral reefs. Deforestation also leads to a greater incidence of floods and droughts in affected regions.

Deforestation contributes to loss of species, with tropical species especially vulnerable to habitat modification and destruction. Migratory species, including birds and butterflies, also suffer. Deforestation can lead to changes in both regional and global climate. When a large forest is cleared, rainfall may decline and droughts may become more frequent in the region.

Deforestation contributes to global warming by releasing stored carbon into the atmosphere and by eliminating a potential sink for atmospheric carbon dioxide.

Desertification

Desertification, affecting 70 percent of the world's dry-lands, is the degradation of once fertile arid and semi-arid croplands, pastures, and woodlands into deserts that have lost their biological or economic productivity. It is due mainly to climate variability and unsustainable human activities such as over-cultivation, over-grazing, deforestation, and poor irrigation practices.

Desertification undermines food production. Stabilization of soil against water and wind erosion is diminished. Degraded land may cause downstream flooding, reduced water quality, sedimentation in rivers and lakes, and the accumulation of silt in reservoirs and navigation channels. It can cause dust storms that exacerbate human health problems including eye infections, respiratory illnesses, allergies, and cases of meningococcal meningitis. Critical habitat for plant and animal species is lost as desertification proceeds, leading to economic losses, including those from declining tourism.

Urbanization

The world's human population is becoming increasingly urban. Land-use changes and pollution associated with urbanization cause the loss of plant and animal habitat and diminish stabilization functions. For example, urbanization often leads to increased erosion and reduced natural watershed control of floods. The filling in of wetlands for urban expansion eliminates their water cleansing function.

Wetland drainage

Over the 20th century, some 10 million square kilometers of wetlands have been drained across the globe, an area about the size of Canada. In the lower 48 states of the U.S., drainage has reduced wetland areas by half, mostly for agriculture. In the process, critical wildlife habitat has been lost, as have floodplains, which are safety valves for flood events and natural filters for flowing waters.

Pollution

Pollution of air, rain (and snow), surface waters, and the land diminishes ecosystem services in many ways. The air pollutant ozone, for example, can reduce growth of agricultural crops and plants in natural ecosystems. Pollution of rain with sulfur and nitrogen compounds results in acid rain that damages plants, impoverishes soils, and acidifies surface waters, killing plant and animal inhabitants. Nitrogen pollution causes harmful algal blooms that deplete the water of oxygen, sometimes severely enough to cause major fish kills. Heavy metals from smelters accumulate in soils, killing plant life and thus creating erosion problems. Persistent organic pollutants such as DDT and PCBs can alter food webs and thereby diminish the ability of ecosystems to deliver services such as pest control.

Dams and water diversion

Dams and diversions change the natural flows of rivers, altering the quality of aquatic habitat and causing species losses. Reservoirs created by dams destroy former land plant and animal habitats, degrading natural beauty and compromising certain forms of recreation. In arid regions, reservoirs lead to greater water evaporation, resulting in increased salinity. When this water is used for irrigation, salt accumulates in the soil, resulting in a decline in crop yields, and in extreme cases, rendering the soil unfit for agriculture.

Invasive species

By affecting ecosystem functions, for example, by altering the food web, invasive species reduce the ability of ecosystems to deliver life-sustaining services.

Lake Victoria, bordered by Kenya, Uganda, and Tanzania, is an essential source of water and fish protein for the surrounding human population. Invasive species and excess nutrient enrichment have transformed Lake Victoria from a clear, well-oxygenated lake with an incredible diversity of cichlid fishes to a murky, oxygen-depleted, weed-choked lake with reduced fish diversity (dominated by predators). The changes have been so dramatic that the ability of the lake to meet human needs is now threatened.

Suggested Readings

Aber J, Melillo J. 2001. *Terrestrial Ecosystems* (Second Edition). Academic Press, San Diego, CA.

Baskin Y. 1997. *The Work of Nature*. Island Press, Washington, D.C.

Burger J, et al (eds.). 2001. *Protecting the Commons.* Island Press, Washington, D.C.

Daily G (ed.). 1997. *Nature's Services.* Island Press, Washington, D.C.

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chapter 3 **Medicines from Natural Sources**

Figure 1 *Taxus brevifolia* (Pacific Yew Tree).

From Charles Sprague Sargent, Silva of North America, illustrated by Charles Edward Paxon, Vol. X, Houghton, Mifflin & Co., Cambridge, 1896, Plate DXIV

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 sempevirens* (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* (Quinhaosu) 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 tax-oids have been produced by semi-synthetic conversions of a precursor compound found in renewable yew tree needles. The paclitaxel story illustrates the great impor-tance 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.*
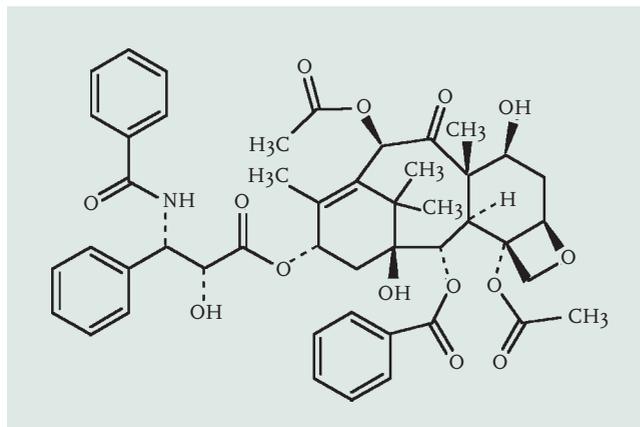
South American Indigenous Knowledge and Medicinal Plants

Unlike the case in Asia and the Indian subcontinent, where written records were kept about medicines, knowl-edge about the use of specific plants for treating diseases in South America was mostly passed on orally among indigenous peoples. Below are two examples of materials that are currently used, both in the countries of origin

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 curares. 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 *Chondodendron* that are the most common curares, and which, because of their observed ability as neuromuscu-lar 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 num-ber 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 the need for 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 Sjogren'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 per-spective 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 ß-lactam antibiotics)

In 1928, Alexander Fleming noticed that a fungus, *Pencillium notatum,* that had contaminated one of his cultures of staphylococcus bacteria, killed the bacteria adjacent to it. A decade later, the systemic drug peni-cillin 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 ß-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 ß-lactam structure, whilst still maintaining activity, medicinal chemists were able to synthesize over 40,000 active ß-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.
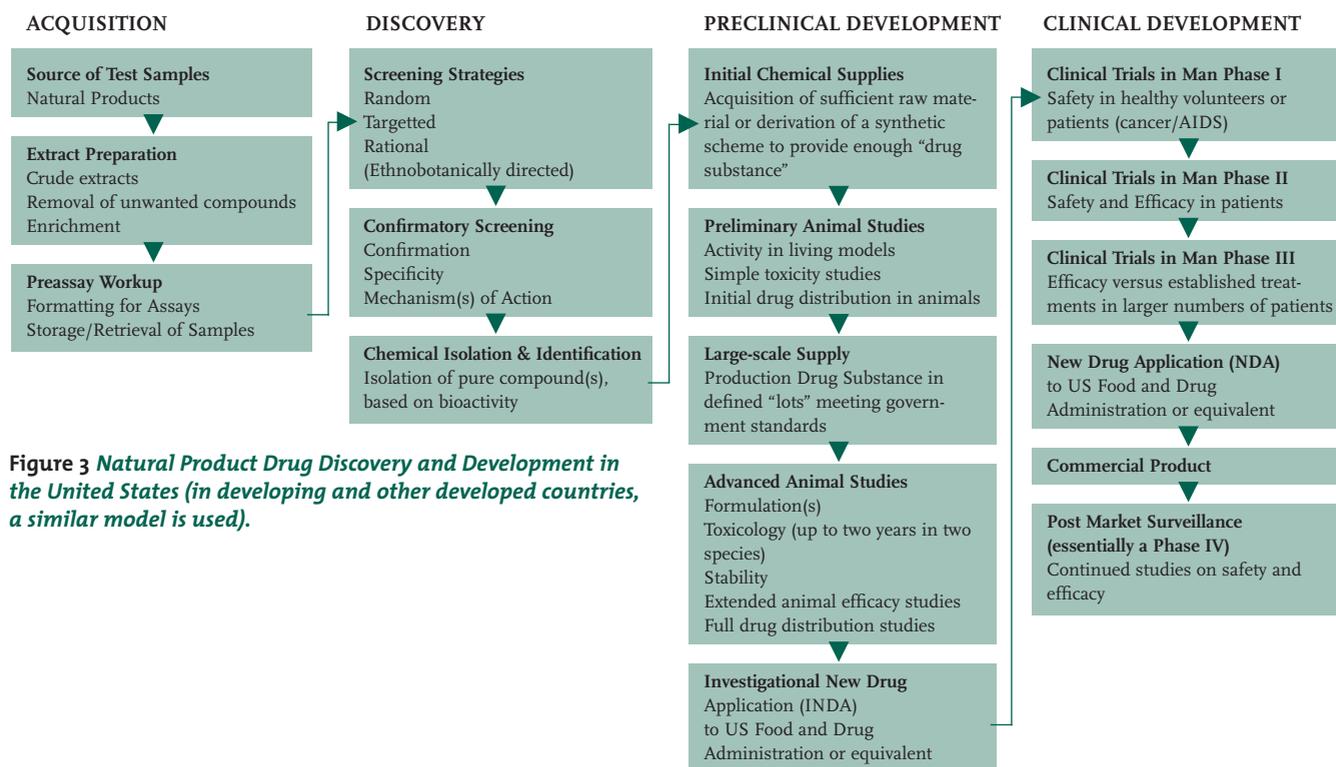
ACQUISITION

Source of Test Samples
Natural Products

Extract Preparation
Crude extracts
Removal of unwanted compounds
Enrichment

Preassay Workup
Formatting for Assays
Storage/Retrieval of Samples

DISCOVERY

Screening Strategies
Random
Targetted
Rational
(Ethnobotanically directed)

Confirmatory Screening
Confirmation
Specificity
Mechanism(s) of Action

Chemical Isolation & Identification
Isolation of pure compound(s), based on bioactivity

PRECLINICAL DEVELOPMENT

Initial Chemical Supplies
Acquisition of sufficient raw material or derivation of a synthetic scheme to provide enough "drug substance"

Preliminary Animal Studies
Activity in living models
Simple toxicity studies
Initial drug distribution in animals

Large-scale Supply
Production Drug Substance in defined "lots" meeting government standards

Advanced Animal Studies
Formulation(s)
Toxicology (up to two years in two species)
Stability
Extended animal efficacy studies
Full drug distribution studies

Investigational New Drug
Application (INDA)
to US Food and Drug
Administration or equivalent

CLINICAL DEVELOPMENT

Clinical Trials in Man Phase I
Safety in healthy volunteers or patients (cancer/AIDS)

Clinical Trials in Man Phase II
Safety and Efficacy in patients

Clinical Trials in Man Phase III
Efficacy versus established treatments in larger numbers of patients

New Drug Application (NDA)
to US Food and Drug
Administration or equivalent

Commercial Product

Post Market Surveillance (essentially a Phase IV)
Continued studies on safety and efficacy

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 cover photo and 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 Effiks used to collect the beans from a plant later named *Physostigma penenosum* 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).*

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 thiocyclam) 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®.

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

Figure 1 *Polar bear mother and cubs, Canada.*

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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 *Drosophilia 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, antidepressants, 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,* and most likely considerably more with the laboratory mouse and the sea squirt *Ciona intestinalis,* the 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 a vertebrate or an invertebrate animal, or a plant, about half of the DNA can be classified as shared among many species, and as 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 diseases, about two thirds have corresponding genes in the fruit fly, and a larger percentage in the mouse. As a result, we can study in other simpler organisms those biochemical and physiological processes controlled by the genes we share, and can arrive at insights about human health and disease that would be very difficult to achieve by studying ourselves.

Most species used in biomedical research are extremely common in nature and are not at all endangered. These organisms are included in this report to illustrate the invaluable information they provide for human medicine, and to make the point that other species, some not yet even identified, may be similar encyclopedias of medical knowledge. Other species or families of species used in research are endangered, some critically so. If they are lost, they will take with them the anatomical, physiological, and behavioral

Table 1 *Major Medical Developments Dependent on Animal Research.*

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

lessons they contain. Some of these lessons may be found in other organisms; others may not. The exquisite complexity of most organisms is the result of millions, or hundreds of millions, of years of evolutionary experiments. We learn both from the similarities between other organisms and ourselves, and from the unique gifts their physiology and behavior provide. In this way, the crisis of biodiversity loss represents a crisis for biomedical research, the full magnitude of which can only be guessed at.
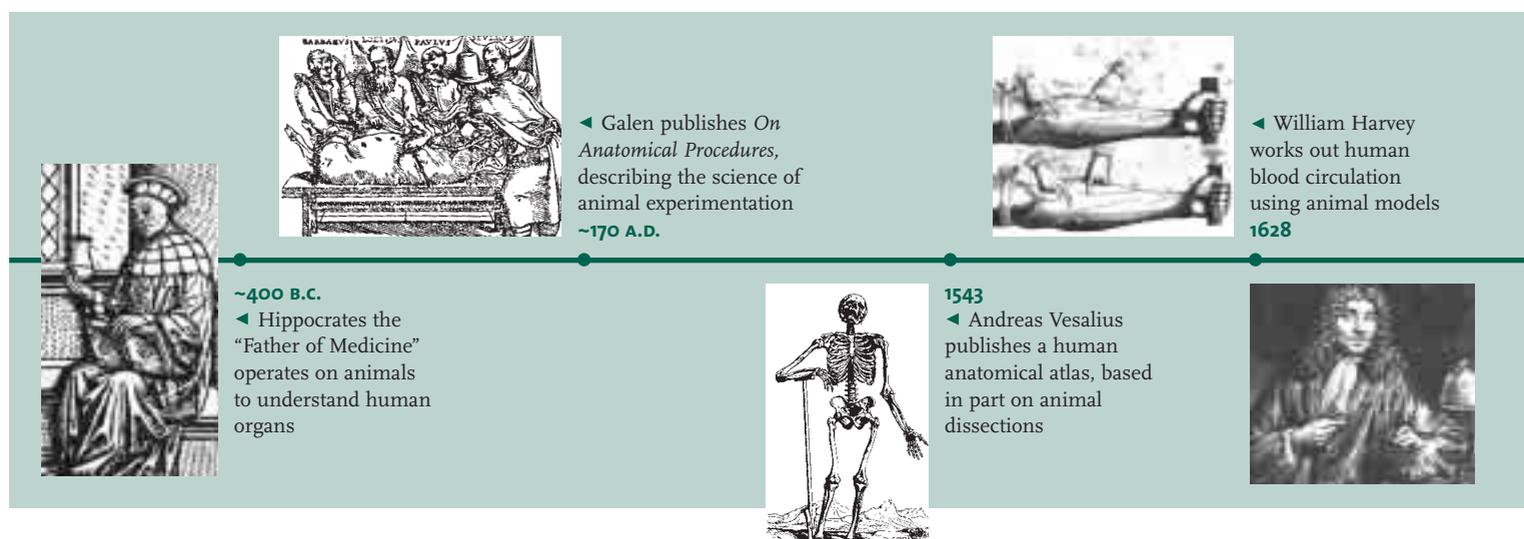
A Brief History of Biomedical Research
(see Figure 2)

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

Figure 2 *Time Line—Historical Medical Milestones Relying on Research with Animals, Plants, and Microbes.*

◄ Galen publishes *On Anatomical Procedures,* describing the science of animal experimentation
~170 A.D.

◄ William Harvey works out human blood circulation using animal models
1628

~400 B.C.
◄ Hippocrates the "Father of Medicine" operates on animals to understand human organs

1543
◄ Andreas Vesalius publishes a human anatomical atlas, based in part on animal dissections

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. Tyzzer 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 an analysis of mammalian physiology, biochemistry, and pathology began.

◄ Ether first used as general anesthetic in surgery after experiments on dogs
1846

► Gregor Mendel publishes work on heredity based on experiments with peas
1865

▼ Louis Pasteur discovers that micro-organisms caused disease, and develops methods of immunization, experimenting with poultry, sheep, horses, and dogs
1885

Late 1600s
Marcello Malpighi and
◄ Antoni van Leewenhoek independently develop the microscope to study cells of plants, animals, and microbes

1865
◄ Claude Bernard elucidates functions of pancreas, liver, and vasomotor nerves based on animal observations

Two themes dominated the first 50 years of mouse genetic research. One was the study of genetic factors that determined susceptibility to transplanted tumors. The other was the effort to analyze the genetic bases for differences in the incidence of spontaneous tumors, which eventually led 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 for 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 those 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 our 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 very limited, and because of disease and the 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 somewhat 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 selectively 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 highly 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.

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 equiva-lent of eighteen times their weight in gold.

The denning bear is the only mammal that fasts for 150 days while maintaining a normal body tempera-ture (~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 virtually 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 osteo-porosis, 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 has also restored normal bone for-mation 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 more than 28 million people, a major proportion of which are post-menopausal women, causes more than 1.5 million bone fractures and 70,000 deaths each year, and costs the U.S. econo-my U.S. more than $13.8 billion annually. Insights derived from denning bears could lead to new treat-ments 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 guinea pig, a mammal which neither hibernates nor dens. 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 immunodeficiency viruses (SIV), a family of viruses that share DNA sequences with human immunodeficiency 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 immunodeficiency 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 at that time. 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 some 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 (RBCs) 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 RBCs. These antibodies cross the placenta, coat fetal RBCs, and cause their destruction. To prevent anemia and survive, the fetus must generate new RBCs 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.

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chapter 5 # Ecosystem Disturbance, Biodiversity, and Human Infectious Diseases

Figure 1 *Urban rice cultivation, Bouake, Côte d'Ivoire. Breeding sites for* Anopheles gambiae *vectors of malaria expand with urban rice growing.*

David H. Molyneux

Introduction

Increasingly, human activities are disturbing both the structure and functions of ecosystems and altering native biodiversity. Such disturbances reduce the abundance of some organisms, cause population growth in others, modify the interactions among organisms, and alter the interactions between organisms and their physical and chemical environments. These disturbances have consequences for human infectious diseases whenever they influence, either directly or indirectly, the organisms involved in the maintenance or transmission of infections. The organisms include: pathogens (the infectious agents); their arthropod or other animal vectors (organisms that transmit the pathogens to humans); the reservoir species that serve as hosts for populations of pathogens outside of humans; and the other organisms within ecosystems and landscapes that support in various ways the interactions among pathogens, vectors, and reservoirs. The sheer diversity of human infectious agents and resulting diseases makes it difficult to generalize about the ways in which ecosystem disturbances and changes in biodiversity may influence human health. Nevertheless, some common patterns exist, and some general principles are beginning to be identified. Chapter 5 explores these patterns and principles, using both descriptions of general themes and a variety of case studies. We provide examples that illustrate the effects of disturbances as well as some of the ecological pathways studied to date.

Human infectious diseases can be categorized according to: (1) the type of pathogen—prions, viruses, bacteria, fungi, or parasites (protozoa and worms); (2) the animal source (or "reservoir") of the infectious agent, i.e. either nonhuman (zoonotic) or human (anthroponotic); (3) the route of transmission of the agent, e.g., air-, food-, soil-, or water-borne; or vector-borne; and (4) within vector-borne diseases, the animal group identity of the vector. Both the source of the pathogen and its route of transmission influence how much ecosystem disturbances and changes in biodiversity affect disease dynamics.

Ecosystem Disturbances and Their Effects on Infectious Diseases

Ecosystems are subject to numerous types and intensities of disturbance, many of which are natural. The focus of this chapter is on those disturbances caused by human activities (i.e. those that are anthropogenic). Some human activities have immediate effects on one ecosystem that later extend to others, and can therefore be considered both a disturbance *per se* and a driver of other disturbances. An example is human-accelerated climate change that can cause drought in a region, which itself constitutes a disturbance, but which also can make the ecosystem more vulnerable to erosion or intense fires, other disturbances. Thus, for our purposes, an ecosystem disturbance can be defined as a human-induced or human-accelerated impact on an ecosystem that changes either the composition or functioning of that ecosystem beyond some baseline or background level of natural disturbance.

Ecosystem disturbances include: (1) changes to the local temperature regime (i.e. its average or its degree of variability); (2) changes in the water cycle—in the timing, intensity, and spatial distribution of precipitation; (3) habitat destruction, fragmentation, simplification, or conversion—particularly through deforestation and reafforestation; (4) changes in the distribution and availability of surface waters, through impoundments, e.g. dam construction or irrigation; (5) agricultural land uses, including for both livestock and crops (such as caused by intensive livestock rearing and monocultures); (6) changes resulting from the deposition of chemical pollutants, including pesticides and excessive nutrients; and (7) the effects of urbanization.

Ecosystem disturbances can affect the risk of acquiring infectious diseases directly, or they can do so indirectly through their impact on the biodiversity of infectious agents, reservoirs, and vectors. An example of the latter is forest destruction and fragmentation in United States landscapes causing the loss of some species of predators of, and competitors with, white-footed mice. The loss of these predators and competitors appears to be responsible for chronically high population densities of mice in remnant forest fragments, which, in turn, increases opportunities for tick vectors to acquire infectious agents (i.e. the bacteria that cause Lyme disease) from the mice and therefore the likelihood of human disease **(see Figures 2 and 3).** In the general case, as top predators are typically more vulnerable to habitat destruction and fragmentation and are often effective in regulating the population size of prey species that serve as reservoirs of disease, one can see how these ecosystem disturbances can affect

Figure 2 *Photomicrograph of* Ixodes scapularis, *the primary tick vector of Lyme disease in North America. Shown is a nymph, the life stage responsible for most cases of Lyme disease in people.*

Figure 3 *White-Footed Mouse. The mouse is a natural reservoir for Lyme disease, Ehrlichiosis, anaplasmosis, bartonellosis, hantavirus pulmonary syndrome, leptospirosis, cyrptosporidiosis, and babesiosis.*

patterns of other human infectious diseases as well. Examples of direct and indirect impacts of some of these categories of disturbance are given below.

Deforestation

The impact of deforestation and associated reafforestation can be organized according to the following principles:

- **The role and behavior of animal reservoir hosts, vectors, and humans (including their immune status) are key determinants in the transmission of infection to humans exposed within the forest and at its interface.** For example, in the cases of leishmaniasis, yellow fever, trypanosomiasis (both African sleeping sickness and Chagas disease), and Kyasanur Forest Disease, deforestation can result in humans coming into closer contact with vectors at the edges between forests and human settlements. Similarly, some animal reservoir hosts increase in abundance near these edges, increasing the risk of human exposure to the pathogens **(see Figure 4).**

- **Forest-related activities, such as clear-cutting, road building, and mining, may increase exposure to some human vector-borne diseases.** For example, exposure to the vectors of yellow fever, leishmaniasis, and malaria is often increased for people engaging in these activities due to an increased probability of exposure to the vectors.

- **The destruction of forest habitat may result in the eradication and replacement of the dominant vector species.** Sometimes, the species replacing those that were eradicated are more effective vectors of disease—such as can be seen with Loa loa (tropical eyeworm) and onchocerciasis (river blindness).

- **Deforestation may be accompanied by common patterns of change in the distribution of vectors.** Insect vectors such as blackflies, tsetse flies, and *Anopheles* mosquitoes in West Africa have changed their distributions in recent decades as desertification and the loss of savannah and riverine forests have occurred. These alterations have tended to favor those vector species better adapted to arid conditions.

- **Reafforestation may be associated with a rapid capacity of vectors and reservoirs to adapt to vegetation that is often non-indigenous.** For example, leishmaniasis, malaria, and both American and African trypanosomiasis can increase in incidence in reafforested areas as their arthropod vectors increase, following the replacement of native vegetation by exotic plants that afford better conditions for vector survival or reproduction.

A recent example of the myriad potential impacts of deforestation on disease comes from tropical forests in South East Asia and Amazonia. Logging can change the abundance, the extent, and the quality of aquatic larval habitats for the *Anopheles* mosquito vectors of malaria via the following possible pathways: removal

Figure 4 *Interface between forest and human settlement in Manaus, Brazil. The proximity of housing to forest habitat contributes to outbreaks of* Leishmania guyanensis, *owing to close contact among sandfly vectors, reservoir hosts, and people.*

of overhead trees that had acidified standing water through organic acid deposition, thereby leading to a more neutral pH; removal of understory plants and litter that had served to drain standing water; and increased light and temperatures on the forest floor accelerating photosynthesis by algae. The consequence of all of these changes appears to be an improvement in the habitat quality for larval *Anopheles* mosquitoes, and a higher potential for population growth. Some species of mosquito, like the *Anopheles darlingi,* the most effective vector for malaria in Amazonia, benefit more from such changes than others.

Deforestation can also lead directly to disturbances of the forest floor, providing depressions that catch and hold water and create new sites for the development of mosquitoes.

Water management

Water management associated with irrigation, dams, containers (e.g., discarded automobile tires), and small impoundments (fish farms, local irrigation by micro-dams) generates ecosystem disturbances that often have dramatic effects on infectious diseases, particularly those transmitted by mosquitoes and carried by snails **(see Figure 1).** For example, dam and irrigation projects have caused large and widespread increases in cases of schistosomiasis in the tropics. Schistosomiasis is a parasitic disease of humans in which the parasite uses freshwater snails as intermediate hosts. More than 200 million people suffer from this disease annually, and millions more are at risk. Construction of the Diama Dam in Senegal, 40 km from the mouth of the Senegal River, created an outbreak of intestinal schistosomiasis that affected thousands of people upstream, causing serious health problems in a population that was previously free of the disease. Similarly, the construction of the Aswan High Dam on the lower Nile of Egypt, and the Blue Nile irrigation project in Sudan resulted in millions of inhabitants of the Nile Delta having a high and chronic risk of exposure to schistosomiasis.

Snail populations that are intermediate hosts of schistosomiasis, though often difficult to distinguish from one another on inspection, can be differentiated molecularly where they display significant diversity and have different capacities to act as hosts. Such differences influence the distribution of schistomosiasis in several sites in Africa, as the distribution of snail populations is determined by differences in water and land environments in those sites. In Lake Malawi over-fishing had reduced populations of snail predators, resulting in greater snail host numbers and a much increased prevalence of schistosomiasis.

Water management may also cause serious problems with malaria unless the problems are anticipated in the construction design. In the 1990s "irrigation malaria" was endemic and widespread in a population of about 200 million people in rural India. The cause was attributed to poorly maintained irrigation systems, a lack of health impact assessment and necessary amelioration measures, uncontrolled local irrigation, seepages and poor drainage, and a rise in water tables (associated with the irrigation) that resulted in conditions suitable for the breeding of the major vector *Anopheles culicifacies*. These developments also led to the creation of slow running streams favored by *Anopheles fluviatilis,* another major vector.

Agricultural development

Agricultural development is a type of ecosystem disruption that can have profound consequences for human diseases. Livestock and game form a key link in a chain of disease transmission from wildlife reservoirs to humans. This is especially relevant to emerging diseases, almost three quarters of which are zoonotic. Thus, changes in livestock management can have serious consequences for human health by promoting the emergence of new pathogens and the re-emergence of old ones. For example, *Salmonella enteritidis* recently emerged as a major egg-associated pathogen globally. Epidemiological data suggest that *Salmonella enteritidis* filled an available ecological niche vacated following the widespread use of antibiotics, which effectively eradicated *Salmonella gallinarum* from large poultry farms. Infection of poultry with *Salmonella gallinarum* prevents colonization by *Salmonella enteritidis,* but because *Salmonella gallinarum* has no reservoir other than domestic fowl, once this bacterium is eliminated, it is highly unlikely to be reintroduced. In contrast, *Salmonella enteritidis* is harbored by rodents (as well as by domestic fowl), from which it continually re-infects poultry flocks.

Another example of increased human disease associated with agricultural practices is the evolution of new, virulent forms of the influenza virus, with serious consequences for human health worldwide. Influenza viruses circulate in domestic fowl (e.g., ducks) with no apparent health effects for these hosts. When ducks are maintained in proximity to pigs, however, influenza virus is transmitted to the pigs, which can serve as vessels for mutation and evolution of the virus, sometimes into highly virulent forms that can be transmitted to humans. The example of influenza, in which different species of domestic animals are housed in close physical proximity, exchange pathogens, and pave the way for the evolution of new, virulent forms, appears to be representative of other animal-derived diseases of humans as well.

Analogous to the situation when humans enter recently cleared forests, subjecting themselves to diseases typically limited to wildlife, livestock themselves can be exposed to new and increased disease threats when human populations move their grazing areas into recently cleared forest, with major ramifications for local economies.

Fires

Evidence is accumulating that smoke and haze from the massive forest fires in Southeast Asia, associated with the El Niño Southern Oscillation (ENSO)-linked droughts of 1997–98, resulted in the widespread failure of tropical forest trees to flower and produce fruit. As an apparent consequence of this fruiting failure, fruit bats (family *Pteropidae)* altered their feeding patterns and, in some areas of Malaysia, concentrated their activity on fruit trees that were maintained on large pig farms. The fruit bats are the natural reservoir for a virus, called the Nipah virus, which, while asymptomatic in the bat host, can be virulent in other mammals. Roosting bats in trees overhanging pig enclosures dropped virus-laden feces and urine into the enclosures, exposing the pigs, which apparently then amplified the virus, and transmitted it to humans. Nipah virus is highly pathogenic in people, killing 35–50% of those infected. An outbreak of the disease in 1999, for example, resulted in more than 265 infections and approximately 100 deaths, and led to the massive destruction of Malaysian pigs and the demolition of many pig farms.

Ecosystem exploitation

The demands of growing human populations for food, the building of roads in previously inaccessible forests as a consequence of the activities of logging and mining companies, and increased pressure on agricultural resources have led to a rise in the consumption of wild forest animals ("bushmeat") in many countries. In the forests of western central Africa, the bushmeat trade in primates has been implicated in the emergence of HIV/AIDS in humans, as the simian immunodeficiency viruses (SIVs) were most likely transmitted to humans by blood exposures (see Chapter 4). As blood exposures to primates in these forests continue at an alarming rate with the bushmeat trade, and as there are at least thirty different primate species now known to carry unique strains of SIV, the risk of different HIV/AIDS-like epidemics in the future may be great.

Additional examples of ecosystem exploitation and human disease include: other cases of bushmeat use linked to outbreaks of plague and anthrax in

Madagascar and India, and a rise in intensive shellfish farming in India and Sri Lanka that has led to devastating human exposures to bacterial and viral pathogens, effectively closing down these trades.

Biodiversity Changes and Their Effects on Infectious Diseases

Biodiversity can be defined as variation at all levels of biological organization, from the genes within local populations or species, to the species composing all or part of a local community, to the communities that compose the living parts of ecosystems. Biodiversity that is relevant to infectious diseases can be understood hierarchically—the incidence of disease may be influenced by biodiversity at the level of the genetic make-up and classification of pathogens, vectors, and reservoir hosts, including domestic livestock; by the diversity of habitats; and by variation in human movements and behavior. In some cases, greater biodiversity is likely to be associated with an increased incidence of disease, e.g., there is a greater threat of disease in tropical areas supporting greater pathogen diversity than in species-poor boreal regions. In other cases, greater biodiversity acts as a buffer to disease risk, e.g., when the abundance of rodents acting as reservoirs is regulated by a diverse assemblage of predators and competitors. Moreover, in many cases, *changes in the elements comprising biodiversity* will be more important to disease incidence than diversity per se. For example, the combination of the replacement of native ungulates by livestock, and the invasive growth in abandoned cropland by the non-native plant species *Lantana,* can result in changes in tsetse-fly *(Glossina)* distribution, with consequent outbreaks of African sleeping sickness.

Diversity of vectors and pathogens

The major vector-borne pathogens and the diseases caused by them are concentrated in the tropics, with the majority of important vectors of human and animal diseases being found in the rich biodiverse tropical rain forest ecosystems, woodland savannas, and the edges of these ecosystems. The major insect vector groups— *Anopheles, Aedes, Culex,* and *Mansonia* mosquitoes; *Simulium* blackflies; the new world vectors of Leishmania *(Lutzomyia);* the *Chrysops* vector of Loa loa; and the *Glossina* species which transmit trypanosomes—all contain species which are dependent on forest, woodland savanna, or riverine forest ecosystems. It is the degradation of these ecosystems; the behavior and ecology of the vectors at the forest edges; and the impact of reafforestation on the interactions between humans,

vectors, and reservoir hosts at the boundaries between habitat types (ecotones) that determine the epidemiology of some human infectious diseases. Additional factors are the degree of immunity of local or migrant populations; their nutritional status and their behavior; the interaction with, and behavior of, reservoir hosts; and the availability and effectiveness of surveillance systems and healthcare.

Diversity of habitat elements

An important, though under-recognized component of biodiversity is the number and type of different habitat elements—forest, grassland, edges, corridors, and living or non-living elements within natural and human-influenced landscapes. Human activities can destroy habitat elements (e.g., forest patches), create new elements (e.g., agricultural fields, water bodies, habitat edges), and rearrange their positions and connectedness. Changes in the diversity of habitat elements and their interactions can influence the risk or incidence of human vector-borne disease via several pathways, briefly described below.

First, anthropogenic changes in habitat diversity, such as the clearing of forests to establish villages or agricultural fields, can result in the juxtaposition of humans with forest organisms, increasing the risk for infectious disease. Human encroachment on tropical rainforests, for example, can increase exposure to *Aedes* mosquitoes and the transmission of yellow fever **(see Figure 4).**

Second, changes in habitat diversity can change or reduce species diversity within natural communities of vectors, hosts, and reservoirs, with cascading effects on disease transmission. For example, conversion of the natural pampas habitat in parts of Argentina to maize fields, and the accompanying creation of habitat edges favored the population growth of the mouse *Calomys musculinus*. Because *Calomys musculinus* is the main reservoir for the Argentine Hemorrhagic Fever virus, this alteration is thought to have led to major outbreaks of Argentine Hemorrhagic Fever among residents in these regions.

Third, changes in the relative abundance or spatial positions of habitat elements can affect either the behavior or the population dynamics of vectors, particularly mosquitoes. The behavior of vectors can be changed if new habitat elements, such as thatch roofs or walls of houses, or abundant domestic water containers, induce vectors to disperse from more natural to more anthropogenic habitats. The population dynamics of vectors can be altered when changes in habitat diversity provide new breeding habitats or alter the abundance of their natural enemies or hosts.

Biodiversity of vertebrate communities

Species diversity within communities of vertebrates can provide a strong buffer against disease risk for humans, a phenomenon termed "the dilution effect". For many zoonoses, the most important natural source (or most competent natural reservoir) of the disease agent is a species (often, although not always, a rodent) that is highly abundant, feeds a large proportion of the vector population, and exists in both species-poor and species-rich communities. In species-poor communities, few alternative hosts are available to supply vector blood meals, and the consequence is a high infection prevalence in the vector population, as it is more often feeding upon the reservoir containing the highest concentration of infectious agents, and therefore leads to a high disease risk for people. In species-rich communities, many alternative hosts ("dilution" hosts) will be available to feed, but not infect, vectors, resulting in a lower disease risk. The dilution effect applies to any disease system that has the following four features: (1) a vector that feeds on a wide variety of species; (2) pathogen acquisition by the vector from hosts (as opposed to exclusively from its parents); (3) variation among host species in reservoir competence (i.e. their probability of infecting the vector during its blood meal); and (4) the tendency for the most competent reservoir host to also be the species feeding the greatest proportion of the vector population. When these conditions are met, vertebrate communities with high species diversity will contain a greater proportion of incompetent reservoir hosts that deflect vector meals away from the most competent reservoirs, reducing infection prevalence and transmission risk. The likely possibility that the abundance of competent reservoirs is also reduced in more diverse communities by the presence of predators and competitors, reinforces the impact of the dilution effect on the density of infected vectors, and therefore on the risk of disease exposure.

The dilution effect model appears to apply to such human infections diseases as Lyme disease, cutaneous and visceral leishmaniasis, African trypanosomiasis, Chagas disease, West Nile encephalitis, tularemia, various mosquito-borne encephalitides, Crimean-Congo hemorrhagic fever, Rocky Mountain spotted fever, and various Ehrlichioses. Similarly, it has been observed that with a greater diversity of snail species, some of which compete with the snails that serve as schistosomiasis hosts, there is a lower risk of human exposure to this parasitic disease.

Climate Change and Its Effects on Infectious Diseases

The Intergovernmental Panel on Climate Change has concluded that "most of the climate change observed in the 20th Century is attributable to human activities." For the past 420,000 years, as measured by the Vostok ice core in Antarctica, carbon dioxide (CO_2) has not exceeded 280 parts per million by volume (ppmbv) in the troposphere (lower atmosphere). Today, CO_2 levels are at 370 ppmbv and the rate of change surpasses rates observed in any previous ice core record (IPCC 2001). Moreover, changes in multiple factors (land-use, stratospheric ozone levels, ice cover, and tropospheric greenhouse gas concentrations) have begun to alter the Earth's climate system. These conclusions are based primarily upon so-called "fingerprint" studies, where observed data match computer projections in what are called General Circulation Models. Three of the most prominent patterns of climate change are:

- The warming pattern in the mid-troposphere in the southern hemisphere,
- The disproportionate rise in nighttime and winter temperatures, and
- The statistical increase in extreme weather events.

A growing number of investigators propose that vector-borne diseases, (e.g., involving arthropods and other animals as vectors), could expand their ranges in response to climate change. Models incorporating such factors as temperature-dependent vector reproductive and biting rates, and microorganism reproductive rates uniformly indicate that under global warming scenarios (with atmospheric CO_2 concentrations, for example, twice what they are now), the transmission of diseases by vectors could expand to higher elevations and higher latitudes. Because the extent of this impact is assessed in all the models using average temperatures, rather than the more rapid winter temperature changes, the current models may be underestimating the potential biological responses, especially at high latitudes and altitudes where the increases are greatest. Diseases that are currently exhibiting geographic expansion, evidently due in part to climate change, are dengue fever, some mosquito-borne and tick-borne encephalitides, yellow fever, and malaria. For some of these diseases, the connections between local-scale expansion and local climatic changes have been more strongly established than have those between regional- or global-scale climate and disease. Climate changes associated with ENSO events have also been linked to increased incidences of malaria, dengue, and Rift Valley fever.

The ability of scientists to predict future climatic conditions exceeds their ability to fully assess the nature and strength of the associations between climatic conditions, anthropogenic change, and the incidence of disease. Understanding these associations depends on our first understanding how current patterns of infectious diseases are influenced, directly or indirectly, by current climatic conditions, which remains a major scientific challenge.

Suggested Readings

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The Role of Biodiversity in World Food Production

Figure 1 *Fourteen different species of African bees.*
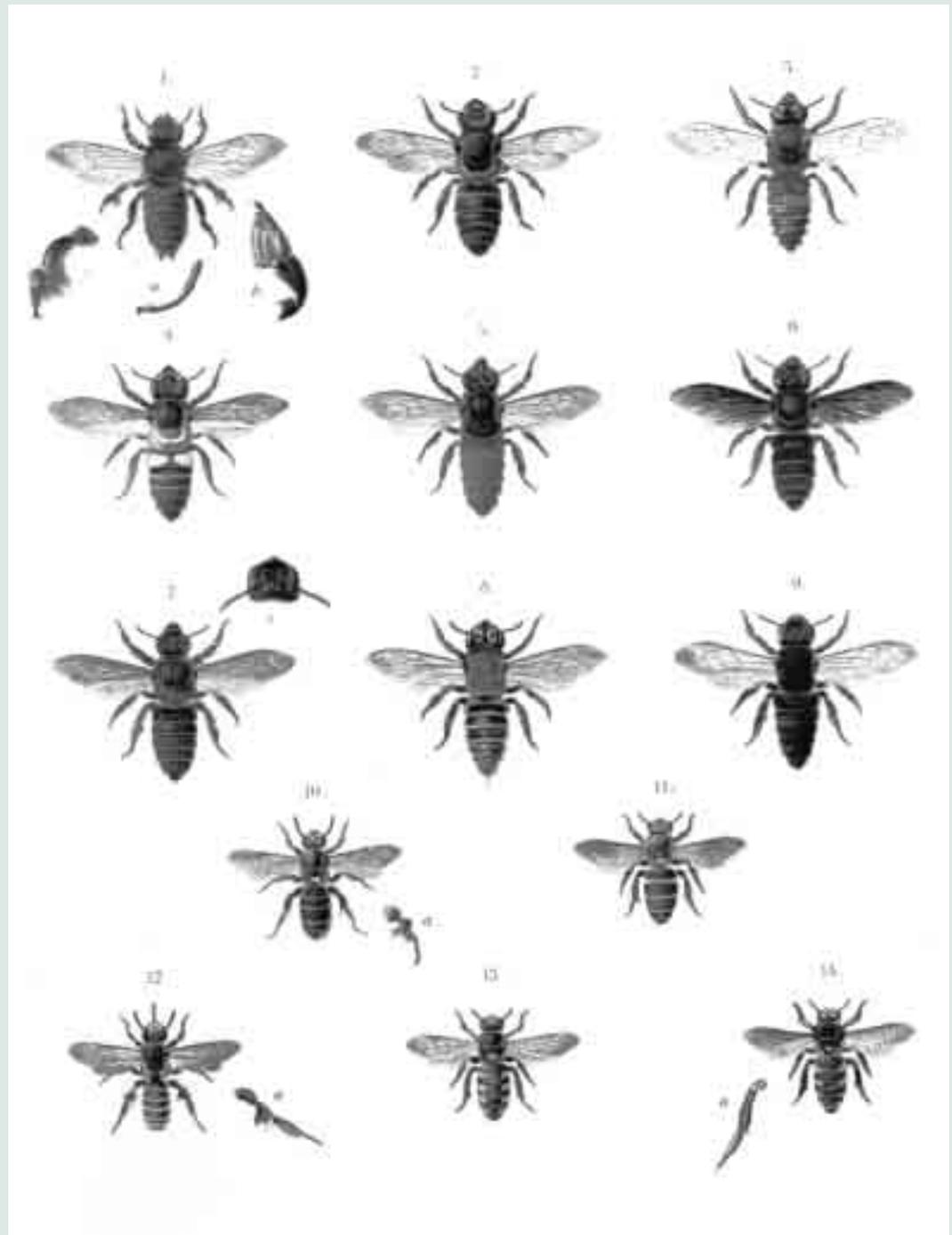
Introduction

Biodiversity plays a crucial role in human nutrition through its influence on world food production, as it ensures the sustainable productivity of soils and provides the genetic resources for all crops, livestock, and marine species harvested for food. Adequate nutrition, in turn, is the prime requirement for ensuring the normal development (both physical and mental) of children, as well as the continuing health and productivity of adults. Reciprocally, world food production has affected biodiversity significantly in the past, and continues to do so up to the present, through its use and odification of biotic resources—on land, in freshwater environments, and in the oceans. The imperative to produce and supply nutritious food for all humans, already numbering over six billion and projected to number eight or nine billion in the course of the 21st century, is certain to become ever more challenging. An equally vital necessity is to devise food production systems that protect and enhance natural ecosystems and their diverse biotic resources. Given the poverty and famine that prevail in many regions, and the foreseen change of the earth's climate (which is inherently unstable in any case), it is an open question whether, and how, humanity can provide for itself while avoiding irreversible damage to natural ecosystems and their biodiversity.

Increasing awareness of the issue, and the development of modern methods of conservation management and of new technologies such as the genetic modification of crops, offer hope for progress in this difficult task. Utilizing the promise inherent in such methods and technologies must, however, be constrained by an understanding of the potential problems and hazards they pose.

Significant Themes

Agriculture depends fundamentally on biodiversity

All the plants whose products are utilized by humans, either directly or indirectly (via plant-consuming animals), were derived originally from wild ancestors. So were all domesticated animals. Those domesticates were selected and bred for their desirable traits, but as environmental circumstances and stresses change, as the requirements and preferences of humans change, and as domesticated organisms themselves are vulnerable to diseases and pests, the need arises repeatedly to breed new varieties. Traditionally, agricultural breeding has been done with the close genetic relatives (either wild genotypes, or domesticated varieties or strains) of the relevant organisms. Different strains may contain different genes, including perhaps genes that impart resistance to certain pests and environmental stresses.

Of all the myriad species of plants or animals whose products can be useful to humans, agriculture utilizes directly only a few hundred. Among those, just 80 crop plants and 50 animal species provide most of the world's foods.

What is not generally appreciated is that those relatively few species depend vitally for their productivity on hundreds of thousands of other species. Among the latter are insects, bats, and birds that pollinate crop flowers, or that help to control pests and diseases that threaten food production. Even more numerous and varied than insects are the microbial species that live on plants and animals, and are especially abundant in the soil. They too help to protect against pests, as well as serve to decompose residues (including pathogenic and toxic agents) and transmute them into nutrients for the continual regeneration of life **(see Table 2).**

In ways both visible and invisible, agriculture thus depends on nature's biodiversity. Hence diminution of that diversity endangers agriculture just as it endangers all the processes of life on earth, which are inherently interdependent.

Marine and freshwater food resources also depend on biodiversity

Biodiversity provides raw materials for the marine food chain and for seafood production, and also influences the capacity of marine ecosystems to perform other environmental services. Harvested marine seafood species now exceed 100 million tons per year and provide about 6% of all protein and 17% of animal protein

Table 1 *Direct and Indirect Effects of Fishing on Species, Ecosystems, and Biodiversity.*

Fishing effect	Impact(s) or consequence(s)
SPECIES EFFECTS	**SPECIES EFFECTS**
Removal of target fish species	>70% of world's commercially important marine fish stocks fully fished, over-exploited, depleted, or slowly recovering; increased likelihood of species loss or extinction caused by over-exploitation
By-catch (1): removal of non-target fish species (e.g. under-sized marketable species or species not currently marketable)	By-catch, or discards, range from 17.9 to 39.5 million tons/year or an average of 27 million tons/year; this replacement of high value fish by 'trash' fish represents enormous wastage of fishery resources
By-catch (2): removal of conservationally important fauna (e.g. marine mammals, turtles, and birds)	Capture of porpoises in gill nets and of turtles in trawl nets not fitted with turtle exclusion devices (TEDs); incidental mortality of species that are long-lived and have low reproductive rates (K-selected species) is a major conservation problem
ECOSYSTEM EFFECTS	**ECOSYSTEM EFFECTS**
Fishing down marine food webs	Stagnating or declining catches, i.e. unsustainability of fisheries, following shift from landings of high trophic level, long-lived species (K-selected species) to low trophic level, short-lived species (r-selected species)
Food web competition	25–34% of primary production in shelf waters (which provide 95% of catches) is harvested, bringing humanity into competition for primary productivity with other apex predators (e.g. seabirds, marine mammals)
Other biological effects on ecosystem structure	Reduced species diversity and local extinctions of both fishery and other (e.g. keystone) species; phase shifts from removal of fish predators of urchins, reducing reef accretion and possibly increasing erosion; interactions between fishing and other agents to impair ecosystem recovery following hurricanes and other natural disasters
Physical effects on ecosystems	Physical (and biological) ecosystem disturbances from trawl nets and dynamite fishing
BROADSCALE EFFECTS	**BROADSCALE EFFECTS**
Evolutionary effects	Trend towards removal of larger sized fish results in populations with slower growth, and a decline in age and/or size at sexual maturity; changes result from compensatory responses as well as genetic effects
Genetic effects	Some evidence of reduced genetic diversity, e.g. orange roughy, virgin stocks of which have been harvested beyond their maximum sustainable yield
Economic and political effects	Conflicts over fish prices, financial insecurity and political dislocation, arising from combination of heavy fishing of shared stocks and inadequate institutional management structures

consumed by humans. These resources include representatives from about nine biologically diverse groups of plants and animals. Fish account for most of the world's marine catches, of which only 40 species are taken in abundance. The highest primary productivity and the richest fisheries are found within Exclusive Economic Zones (EEZs). These narrow strips (200 nautical miles or 370 km wide) of ocean bordering countries are not only the sites of coastal "food factories", but also the areas associated with the heaviest perturbation of the marine environment.

Many human activities, including unsustainable fishing (the U.N.'s Food and Agricultural Organization states that over 70% of the world's fisheries, such as the Northwest Atlantic Northern Cod, are over-exploited); unsustainable mariculture and aquaculture; the degradation of coastal wetlands, estuaries, coral reefs, and mangroves—habitat and nurseries for finfish and shellfish; and the disposal of wastes in the sea lead to an erosion of marine biodiversity **(see Table 1).** These wastes can include toxic substances, such as heavy metals and some organic pollutants (which can become increasingly concentrated at progressively higher levels of the marine food chain), and nutrients discharged from sewage and from agricultural runoff. Such activities can undermine the biophysical cornerstones of fisheries and have other undesirable environmental side-effects.

Of direct concern are species effects, in particular the removal of target and non-target fishery species, as well as fauna in need of conservation. Equally disrupting but less immediate are ecosystem effects, such as fishing down the food web, following a shift of harvested species to lower trophic levels. By removing excessive numbers of predators at the top of

the food web (such as some species of sharks), which serve to cull weak and sick species, humans can damage the health of the entire food web. Physical and biological disturbances—from draggers (which can be as destructive in the oceans as clear-cutting forestry operations are on land), drift nets, and fine-mesh trawl nets, to dynamite and cyanide fishing on coral reefs—can also severely impact ecosystem structure and functions. Broad-scale biological and social effects brought about by fishing carry even more far-reaching consequences. For example, fishing itself can change the age at which sexual maturity is reached, thus affecting the reproductive status of the stock. Hence, fishing may be regarded as a mediator of evolution. Social impacts include conflicts over fish prices and policies arising from heavy fishing and inadequate institutional structures.

Freshwater fisheries are also dependent on biodiversity and highly vulnerable to human disturbance—from the damming and channelization of rivers that damage riverine environments downstream, to the introduction of alien species, to contamination by nutrient discharge and toxic substances. Increasingly, freshwater fish such as carp, tillapia, and catfish are raised by aquaculture, and provide ever larger proportions of protein consumption for local and regional populations in developing countries, particularly in parts of Asia, which produces 90% of the world's aquaculture catch. In China, for example, which accounts for two thirds of global aquaculture totals, herbivorous carp species are extensively and sustainably cultured, often in conjunction with agricultural ecosystems.

## Biodiversity in agriculture performs multidimensional functions

Pure stands of genetically similar, or essentially identical, plants are at greater risk than are genetically diverse stands. Conversely, genetically diverse crops can better survive in heterogeneous environments in which climate and soil conditions fluctuate. Though the latter may not provide yields that are as great in favorable seasons, they are more likely to adapt to varying conditions and to provide adequate yields in unfavorable seasons. Genetic diversity is thus likely to reduce the odds of crop failure and to contribute to greater stability of production. Similar benefits may be inherent in mixed-species and multi-species cropping systems such as are common in subsistence farm units. In contrast, uniform monocultural crops, standing like battalions of identical soldiers in close formation, may produce high yields in favorable conditions but fail badly under the influence of suboptimal or anomalous conditions. Pathogens spread more readily, and epidemics tend to be more severe, when the host plants (or animals) are more uniform, numerous, and crowded. Owing to their high densities and the large areas over which they are grown, both crop plants and livestock are repeatedly threatened by ever new infestations by pests and diseases. Existing pests and diseases are continually evolving strains that overcome the innate defenses of particular strains or breeds, as well as of chemical treatments applied by farmers.

Table 2 *Soil Ecosystem Services Performed by Different Members of the Soil Biota.*

FUNCTIONS	ORGANISMS INVOLVED
Maintenance of soil structure	Earthworms, arthropods, soil fungi, mycorrhizae, plant roots, and some other micro-organisms.
Regulation of soil hydrological processes	Mostly invertebrates like earthworms and arthropods, and plant roots.
Gas exchanges and carbon sequestration	Mostly micro-organisms and plant roots, some carbon protected in large compact biogenic invertebrate aggregates.
Soil detoxification	Mostly micro-organisms
Decomposition of organic matter	Various saprophytic and litter-feeding invertebrates (detrivores), fungi, bacteria, actinomycetes, and other micro-organisms.
Suppression of pests, parasites, and diseases	Mycorrhizae and other fungi, nematodes, bacteria, and various other micro-organisms, collembola, earthworms, various predators.
Sources of food and medicines	Plant roots, various insects (crickets, beetle larvae, ants, termites), earthworms, vertebrates, micro-organisms, and their by-products.
Symbiotic and asymbiotic relationships with plant and their roots	Rhizobia, mycorrhizae, actinomycetes, diazotrophic bacteria, and various other rhizosphere micro-organisms.
Plant growth control (positive and negative)	*Direct effects:* plant roots, rhizobia, mycorrhizae, actinomycetes, pathogens, phytoparasitic nematodes, rhizophagous insects, plant growth promoting rhizosphere micro-organisms, biocontrol agents. *Indirect effects:* most soil biota.

Figure 2 *Soil organisms—The diversity of life in fertile soil includes plants, algae, fungi, earthworms, flatworms, round-worms, insects, spiders and mites, bacteria, and burrowing animals such as moles and groundhogs.*
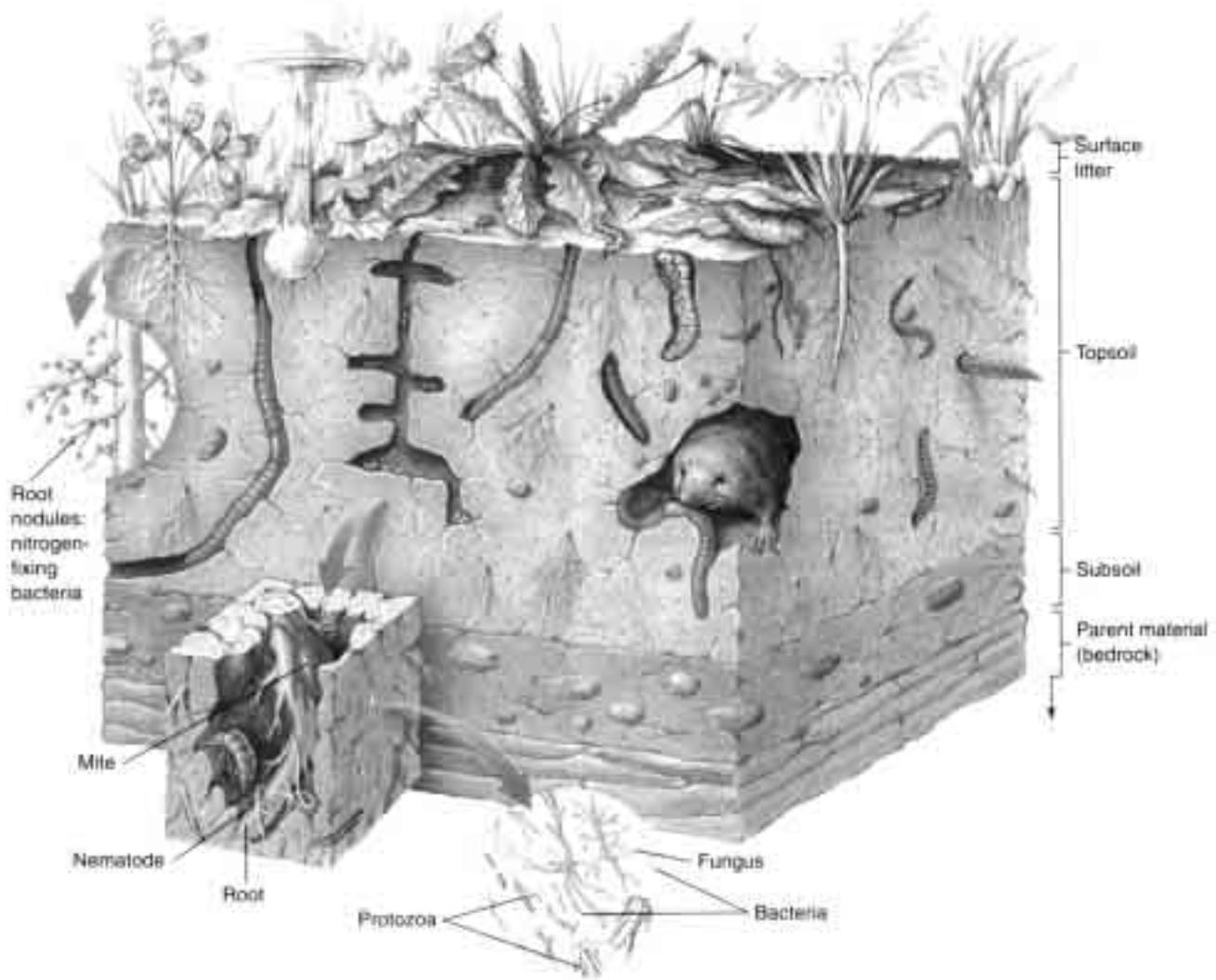
Many historical examples can be cited to prove that monocultural stands or concentrations of crops and livestock with uniform genetic traits, though they may be be more productive in the short run, entail the risk of succumbing, sooner or later, to changing conditions. Catastrophic outbreaks of disease, invasions of insects, and climatic anomalies have caused many wholesale crop and animal destructions in the past. Such episodes have resulted in famine, especially where, in the absence of sufficient diversity, no other varieties or breeds were present that could withstand the destructive outbreaks.

Among the many examples of disastrous out-breaks are the infestation of red rust on wheat in Roman times, the mass poisoning from ergot-tainted rye during the Middle Ages in Europe, the failure of the vaunted vineyards of France in the late 19th century, and the potato famine that hit Ireland in the 1840s and 1850s. The latter was caused by the fungus *Phytophthora infestans,* which attacked the genetically uniform potato stock that served as the mainstay of Irish farms. It caused many deaths and the migration of about half the rural population of Ireland to the United States. Such mass migration from devastated countries to "virgin" lands is no longer possible.

No less vulnerable than crops are domesticated breeds of livestock. When thousands or tens of thousands of animals (such as cows, sheep, hogs, and poultry) are packed into enclosures, diseases can spread epidemically. Examples pertaining to livestock include the outbreak of an avian flu strain in Hong Kong in

1998 (to which humans were susceptible), which led to the death or destruction of millions of chickens. The most recent examples of the sudden spread of animal diseases are the "mad cow" and foot-and-mouth epidemics that afflicted Britain in 2000–2001, and practically devastated the dairy and wool-growing industries there. In the case of "mad cow" disease, or bovine spongiform encephalopathy (BSE), there is also a direct human health impact, with some exposed people developing a variant of Creutzfeld Jacob Disease, a rapidly progressive brain wasting disease that has no cure and that invariably causes dementia and death.

Agricultural productivity and sustainability benefit from the diversity of micro-organisms in many ways. Some bacteria, for example, convert elemental nitrogen from the atmosphere, which cannot be utilized by plants, into soluble nitrogen compounds (e.g., ammonia and nitrates), that can be. In this way, the essential nutrient nitrogen is made accessible to plants. These nitrogen-fixing bacteria may be either symbiotic (living in association with leguminous plants) or non-symbiotic, living free in the soil. Another vital function is fulfilled by mycorrhizal fungi, which live in association with crop roots and facilitate the uptake of phosphorus and other relatively immobile nutrients **(see Table 2 and Figure 2).**

While some plants are self- or wind-pollinated, most flowering plants, including almost all the world's fruit and grain crops, rely on other species for pollination in order to produce fruit and seeds. These pollinators include large numbers of both invertebrate and vertebrate species: bees, wasps, beetles, flies, butterflies, moths, birds, and bats. Many pollinator species are at risk because of human activities, including the destruction of habitat, misuse of pesticides, and the introduction of invasive species. For example, in the U.S., more than 50 pollinator species have been listed as threatened or endangered, and wild honeybee populations have declined by 25% since 1990, in part, because of infestations by parasitic mites. The most important pollinator for agricultural purposes is the honeybee, which supplement the services provided by wild pollinator populations or are the sole pollinators. When pollinators are lost, the losses for agriculture can be catastrophic **(see Figure 1).**

The biodiversity on which agriculture depends in now threatened

There is reason to be concerned, especially over the concentration of genetic resources, agricultural production, and food consumption on three primary crops—wheat, rice, and maize **(see Figure 3)**—which together account for nearly 60% of the calories and some 56%

of the protein people derive from plants. In principle, such a concentration creates vulnerability. One example of the vulnerability of wheat is the recent outbreak of *Fusarium* head blight on wheat and barley in the United States—in Minnesota and in the Dakotas. Many farmers in areas where this infestation has been severe have been forced to abandon farming for lack of alternative crops to grow profitably.

Several anthropogenic factors and processes pose a growing threat to biodiversity in agriculture. First and foremost of these is the extensive destruction of natural habitats, resulting from human encroachment and appropriation of increasing portions of the land surface. The fraction of the Earth's continental surface that is used for agriculture is "only" about 12%. Added to that, however, is an area totaling some 25% that is used for grazing livestock. The picture looks even grimmer if we take into account the large fraction of the Earth's land surface that is desert, tundra, steeply mountainous, or otherwise less productive (hence largely unsuitable for human exploitation). Excluding those areas, the fraction of the earth's biologically productive land surface currently utilized is more than 50%.

Secondly, air pollution, which can lead to toxic levels of tropospheric ozone at ground level and to acid precipitation, and global environmental changes, includ-

Figure 3 *Zea mays* **(Maize).**

ing global warming and associated climate change, and the depletion of stratospheric ozone, can endanger crops and other species in agro-ecosystems.

The third factor affecting biodiversity in agriculture is the trend toward the standardization of crop varieties and of livestock breeds. Not only are the wild progenitors or relatives of crop plants becoming rarer, but even numerous "old" varieties, such as land races developed by generations of indigenous farmers, have been replaced by a restricted number of favored types, whose seeds are sold by major commercial enterprises. Although people in different parts of the world consume the products of about 7,000 species of plants, only 150 or so are commercially important, and just 100 account for 90% of the world's food crops.

The Green Revolution, which did indeed succeed in raising the production of grain (wheat, rice, and maize) in large areas of the world, is now seen to have also had its negative side effects. It promoted the intensive cultivation of specific varieties in monocultural systems, with greatly enhanced usage of chemical inputs (both fertilizers and pesticides on which these crops have become increasingly dependent). As such, it may have contributed to the diminution of agricultural biodiversity and—indirectly—to some degradation of natural resources.

Genetic diversity is also being diminished in livestock. The number of breeds has declined markedly over the decades of the twentieth century. Much of the loss is due to the trend toward the standardized commercial production of chickens and turkeys in factory-like facilities; and of dairy cattle and beef cattle in feedlots. The Holstein breed of dairy cows, for instance, has become the pre-eminent breed worldwide, at the expense of numerous other neglected local breeds. Commercial production methods of livestock are especially prevalent in the vicinities of the world's growing urban centers. The convergence of material inputs (feeds, fuels, etc.) imported into these facilities, and the disposal of wastes from them, produce significant environmental impacts, which are not being properly accounted for in today's so-called "global market economy." Those impacts inevitably include biodiversity losses. Traditional breeds, now considered obsolete by some, are preserved only in isolated spots, and habitats that may still sustain the wild relatives of livestock species are not adequately protected in many centers of origin around the world.

New possibilities of genetic transfer among species present opportunities and risks

Recently, new possibilities have arisen to transfer desired traits (genes) not just between strains of the same species, but even from one species to another,

thus greatly enlarging the range of potential genetic resources available to agriculture (though the new techniques also present new hazards). Nonetheless, breeding plants and animals for agricultural purposes was, and remains, dependent on Nature's rich array of life forms, i.e. on natural biodiversity.

Modern biotechnology, including the generation of genetically modified species of crops, seems to have increased awareness of the value of biodiversity, both within and among species. The very prospect of transferring useful genes to completely unrelated plants greatly enlarges the pool of genes potentially available to crop breeders. This should serve as a further inducement to preserve the full panoply of biodiversity for utilitarian reasons (the anticipated benefit to human society), in addition to the fundamental ecological and ethical reasons. Among the successes cited for biotechnology are the insertion of Bt genes (from strains of the bacterium *Bacillum thuringiensis)* into maize, potatoes, and cotton to impart to these crops an inherent resistance to certain insect pests. Another acclaimed development is the so-called "yellow rice" (or "golden rice"), which enhances the beta-carotene (Vitamin A) content of the otherwise deficient rice crop.

However, the development of biotechnology and genetic engineering is not likely to be problem-free. Behind the hoped for benefits lurk potential pitfalls. Modified organisms may escape from greenhouses and fields into natural, or quasi-natural, ecosystems, and disrupt their biodiversity. Such an invasion of alien species of fish in the context of aquaculture (the raising of finfish, shellfish, and crustaceans like shrimp in cages or other structures in the sea or in fresh water) pose, it is predicted, major threats to wild fish stocks. There are also serious concerns that inserted genes like those expressing Bt toxin will harm non-target species and have unanticipated impacts on agro-ecosystems. Given the complexity of these ecosystems and our incomplete understanding of their dynamics, it may not be possible to design experiments for genetically modified crops that account for all the variables involved or that are sufficiently long term. Moreover, there is some question about the potential for severe allergic responses in some people ingesting genetically modified crops.

Another insidious possibility is that large commercial corporations, under patent laws and the protection of "intellectual property rights," will appropriate the benefits to themselves. Many consider it unfair that the culminated work of generations of farmers, as well as of scientists researching and publishing openly and cooperatively, should now be certified as the commercial property of exclusive groups, whose interests

are to maximize their own profits. Apart from the basic ethical questions this arrangement raises, there is the specific conflict of interest between the proprietary corporations and the most needy people of the developing nations, from whose territory the useful genetic material had (in many cases) been extracted in the first place. Now these nations may well find themselves unable to pay for the same genetic material once it is put into directly useful form (i.e., incorporated into new varieties of crops).

A new agricultural paradigm, based on an agro-ecosystem approach that protects and enhances biodiversity, is now being created

Agriculture has already begun to develop and adopt better methods of production coupled with biological control and conservation, aimed at preserving, even enhancing, the diversity of life on earth. The new approach is impelled by a growing recognition of the indispensable importance of biodiversity to agriculture.

The new paradigm has many facets. One is to provide insurance against the future failure of our currently grown crops and livestock. This can be done by the enhancement of biodiversity, both to allow improvement of, and to discover appropriate substitutes for, those genetically homogeneous varieties.

Another facet of the new paradigm is to maintain natural areas in the vicinity of agricultural fields. Biological control agents (so called because they prey on pests and other enemies of farm crops and animals), as well as pollinators, generally reside in natural or seminatural ecosystems. The previously common practice of eliminating the habitats of these ecosystems, in the belief that such action prevents the invasion of pest species into fields and orchards, may actually do more harm than good, by depriving agriculture of beneficial organisms.

During a major part of the twentieth century, farmers in industrial countries relied primarily on chemical pesticides to control pests. In the last few decades, however, an increasing awareness of the limitations and damages associated with chemical pesticides, as well as of their acute toxic effects for farm workers, and of their potential long term health effects in the general population (as some pesticides accumulate in human tissues) has led to the development of sophisticated techniques of "integrated pest management" (IPM). Such methods are based on the judicious combination of biological controls, together with sparing applications of chemicals only when absolutely necessary. The biological control component of IPM, in turn, depends on ecosystem biodiversity.

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chapter 7 *Policy Options*

Introduction

This report has highlighted the many linkages between biodiversity and human health. To enhance these linkages requires that we consider biodiversity and human health as different aspects of the same issue: that people are an integral part of Nature and must learn to live in balance with its other species and within its ecosystems.

The previous chapters have reviewed the major issues and challenges. This chapter seeks solutions, drawing out policy options for addressing the priority issues identified in the first six chapters. Key targets at the international level include: the World Health Organization (WHO), the United Nations Environment Programme (UNEP), the U.N. Convention on Biological Diversity (CBD), the U.N. Development Programme (UNDP), the U.N. Food and Agricultural Organization (FAO), the World Bank, and the other relevant agencies, international conventions, and non-governmental organizations working on health and biodiversity. At the national level, in addition, key targets include: legislatures, planning agencies, ministries, development agencies, as well as scientists and health professionals.

The policy options we have considered demonstrate how those concerned primarily with conserving biodiversity can make important contributions to human health, and how those concerned primarily with human health can contribute to conserving biodiversity. Particular attention is given to developing countries where local ecosystem goods and services remain vital to people's sustenance and well being.

General Principles

Developing appropriate policy for biodiversity and human health is challenging because:

- Economic, social, and ecological patterns are continuously changing;
- Many policies are interdependent (e.g., legislation on biotechnology may affect both the genetic diversity of crops, the economic returns from bioprospecting, and global trade agreements);
- Many policies are limited in their extent if implemented alone. A concert of policies may be required to fully address an issue (e.g., nutrition is related to agriculture, trade, population, pesticides, and so forth, many of which also affect, and are affected by, biodiversity);
- The range of policy responses is broad and complex, especially if one considers wider development factors, such as poverty.

In view of the above, the policy options suggested here are grouped around "key policy objectives", identified at the beginning of sections, and are designed to provide flexibility for application in different circumstances and by different countries. These options need to be considered as preliminary, as they have not been peer-reviewed, and as the full report on which the final Executive Summary will be based, is still in the process of being written.

The implementation of any policy also requires continuous monitoring and periodic re-assessment to ensure that the policy is adapting to changing conditions of both health and biodiversity. Taking these changing circumstances into account and reducing uncertainty requires further research to help identify future hazards to human health from global environmental degradation, and to suggest appropriate courses of action. However, the need for conducting research should not be used as an excuse to avoid taking appropriate measures in a timely manner. The contribution made by additional data and analysis must be carefully weighed against the potential costs of delaying necessary action.

> *Key policy objective:* **Improve public and institutional understanding of the links between human health and biodiversity.**

The first challenge, and arguably the most important, is to build public and institutional support for productive action on biodiversity and human health. Only if the public sees the importance of considering these issues together will it be possible to generate the kinds of polit-

ical and institutional support that will be required. This will also require stronger collaboration between the health and environment sectors.

Policy Options

- Mobilize public concern about human health and biodiversity issues. Produce and articulate information concerning biodiversity/health linkages through workshops, local support programmes, international conferences, university curricula, and publication in the scientific literature and popular press.
- Enhance collaboration between health and environment sectors, organizations, and ministries. Work with conservation and environmental groups and major international agencies, including the WHO, UNEP, CBD, FAO, UNDP, the World Bank, and regional development banks interested in the relationship between human health and biodiversity, to address the main forces driving biodiversity loss;
- Enhance the channels of communication and collaboration between grass-roots environmental and health organizations.
- Ensure that biodiversity and human health issues are considered comprehensively and together when planning and implementing development projects.

Chapter 1: Biodiversity

> *Key policy objective:* **Conserve global biodiversity by controlling those factors that threaten it, including habitat loss, invasive alien species, pollution, and global climate change.**

Policy Options

- The area of terrestrial ecosystems that is effectively protected needs to be greatly increased. The most important priority is the roughly one million square kilometers of the 25 "biodiversity hotspots" that are not yet protected.
- There needs to be a cessation of unsustainable forestry practices and retention of all the world's remaining wilderness forests, and consequent protection of their indigenous peoples.
- Marine protected areas—especially coral reefs—need to be greatly expanded, both as a means to protect biodiversity and to effect better fisheries management.
- Invasive species are a leading cause of the loss of biodiversity and create massive economic problems on land, in freshwater, and in the oceans. Deliberate transport of species outside their native ranges should occur only when extensive prior experience

suggests the species will have few effects, and should never be permitted when prior experience demonstrates severe effects. Quarantines to prevent accidental introductions should be enhanced.
- Perverse economic subsidies harm natural ecosystems and do so at great economic cost. Such subsidies should be reduced and shifted to comparable economic supports that are environmentally benign.
- Proper attention must be paid to global warming, since it has the potential to disrupt terrestrial, freshwater, and marine ecosystems to a massive degree.

Chapter 2: Ecosystem Services

> *Key policy objective:* **Preserve the integrity of natural ecosystems and the goods and services they provide.**

Policy Options

- There is a clear need to maintain natural, well functioning ecosystem services and to restore impaired ones. Ecosystem services are the planet's life support system, and our lives, indeed all life, would be impossible without them.
- The first step is to identify and catalogue what these services are and where they operate. We must then evaluate how well they are working relative to their potential and to our needs. To make these judgements, we will need to mine, re-organize, and evaluate historical records of ecosystem function.
- In cases where ecosystem services have been impaired, we must take steps to restore them. This will require substantial ecological knowledge of the biological, chemical and physical aspects of ecosystems that combine to yield life-essential services. We will have to define the minimum area needed to provide a given service and how actions to restore one service might affect others. We must maintain the complex mix of co-benefits resulting from ecosystem structures that have evolved over millennia.
- Many argue that environmental protection makes good economic sense. Implicit in this argument is the desire to place economic value on ecosystem services. In a few cases this has been done successfully, but methods for valuation of ecosystem services are still in a very early stage of development. Environmental economists and ecologists must develop standard approaches. With appropriate valuation procedures available, policy makers should be able to incorporate ecosystem services into the cost/benefit analyses that are increasingly guiding decision-making processes.

- Not all ecosystem services, however, can be reduced to monetary values. Some "life-fulfilling" functions such as aesthetics, that can promote emotional well being, are in the truest sense of the word "priceless." Others are so vast, or so complex, or so inadequately understood that it makes little sense to assign to them a monetary value, as to do so implies that they can be replaced by human invention. A recognition that they cannot be should convince policy-makers and the world's public of the urgent need to preserve the functioning of natural ecosystems.

Chapter 3: Medicines from Natural Sources

Key policy objective: Conserve and sustainably manage species important for medicinal use, in particular by promoting access and equitable benefit-sharing regarding traditional knowledge and resources

Policy Options
- There is a need to balance the valid concerns of countries and indigenous peoples for the preservation of their natural resources and of their social and cultural values, with the pressing need for society to be able to use those resources to discover new pharmaceuticals to relieve human suffering.
- There is also a need to balance the rights of source countries and peoples for adequate compensation and for a voice in the development of any new medicines, with the rights of pharmaceutical companies to market their discoveries, and to maintain patents that allow them to generate sufficient revenue to continue the development process.

> A major problem that often clouds the drug discovery process is the widely held perception that all samples from Nature have very high value. Unfortunately, this is not the case; the vast majority of samples prove to have no known biological activity and never become commercial medicines. It takes thousands of compounds for one to become a potential drug candidate, and for every 50 that reach this status, only one makes it to market. A recent analysis of the numbers of new pharmaceuticals approved world-wide for all diseases from 1983 to 2000, for example, demonstrated that on average only seven to eight new drugs per year came from natural products despite large scale global screening efforts, and that most of these were microbial. Moreover, in general there is a high financial risk for companies pursuing drug development, for in the rare cases when activity is found, the costs of developing this initial discovery into a commercial drug is currently in excess of U.S. $400 million.

- Another important area is that of patents, permits, and compensation for source countries. Because there is often little distinction made among the various steps along the way towards marketing a new drug, permits and payments are generally not graduated and can often be quite restrictive from the beginning of the process, inhibiting bio-discovery. An optimal system might be one that had less restrictive permitting for initial research and screening purposes, followed by more restrictive permitting when a compound is patented and moves to clinical trials, with graduated milestone payments to source countries along the clinical trial pathway.
- Concerns that an organization might patent a compound and develop it without notifying the source country can be overcome by the use of database searches of the patent literature at reasonable cost. Alternatively, there could be a central registry of patents resulting from such international natural drug development, perhaps through a U.N. agency such as the WHO or the CBD.
- Source countries, their scientists, and Western organizations can establish mutually beneficial programs that involve technology transfer and collaborative efforts, with an absolute requirement that any organization that develops a drug from a source country's material must involve the source country in the ultimate development. The process that the U.S. National Cancer Institute (NCI) went through with the government of Sarawak in the development of the potential anti-HIV drug Calanolide provides a good model for what can be achieved with goodwill on both sides.

> In 1987, a collection of leaves and twigs from the tree, *Calophyllum langierum* was made in Sarawak by John Burley a Harvard botanist working for the University of Illinois at Chicago (UIC) under a NCI plant collection program. NCI chemists identified a novel agent (named Calanolide A) in these materials that had potent anti-HIV activity (it was a non-nucleoside reverse transcriptase inhibitor). When NCI required more of the leaves and twigs to further investigate the compound, it was discovered that the original tree was gone, and that other *C. langierum* trees could not be found. In conjunction with the Government of Sarawak, NCI through UIC, commissioned a thorough investigation of similar species in the same general area and ultimately discovered that a closely related species *C. teymannii* produced an isomer, Calanolide B in its latex that could be obtained by "tapping" the tree like a rubber tree. Although Calanolide B was not as potent as Calanolide A, it still had anti-HIV activity and the same mechanism of action. In order to further protect the rights of Sarawak, NCI and the Government of Sarawak established a formal agreement based upon the NCI's Letter of Collection (which was first used in 1989, three years before the Convention on Biological Diversity) that required any organization that licensed the Calanolides from NCI (who by US law had

patented them), would have to negotiate an agreement with the Sarawak government as a condition of the license. Such an agreement was signed by MediChem Research that resulted in a 50:50 joint venture, Sarawak-MediChem Research, to develop these agents, which are currently in clinical trials.

- Finally, the collection and development of samples must be scientifically managed and carefully monitored so that the natural functions of the ecosystems from which samples are taken is maintained and its biodiversity conserved. Numerous examples, such as the sustainable management of collection of the soft coral *Pseudopterogorgia elisabethae f*rom coral reefs near Grand Bahama Island in the Caribbean to produce enriched extracts containing anti-inflammatory agents, the pseudopterosins, illustrate that it is possible, with scientific understanding of an ecosystem and careful management, to develop a commercial product while maintaining the integrity of an ecosystem.

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

> *Key policy objective:* **Conserve and sustainably manage species important for medical research.**

Policy Options
The collection of wild plants and animals for research purposes should require verification to ensure that such collection is sustainable. This involves action at several levels including:

- Biomedical companies, other research institutions, and researchers should develop codes of conduct for the responsible collection of these organisms.
- Countries need to regulate the collection and trade of their wild species. Appropriate measures might include: establishing a permit system for harvesting species from the wild, developing national-level databases to bring together information on the identity, distribution, demography, and conservation status of medicinal plants and animals, and promoting the involvement of local communities and local government units in the organization of such databases.
- There needs to be enhanced awareness among traditional medical practitioners and local communities of the problems caused by over-harvesting, poaching, and the loss of traditional knowledge. This awareness can be further enhanced through creating incentives for local communities to contribute to long-term

conservation of resource populations through establishing some legal responsibility and tenure over these resources.
- To reduce the potential for over-exploitation of wild species, research institutions should finance the development of techniques to culture those organisms collected in the wild, and of methods to synthesize chemical compounds of interest early in the research.
- These institutions should also promote and support sustainable collection in source nations, particularly in developing countries, by providing funds that support research and monitoring activities, and the establishment and maintenance of protected areas.

Other suggested policy options:
- All internationally traded organisms, whether or not they are currently listed as threatened, should be monitored by the Convention on Trade in Endangered Species (CITES), so that there will be baseline records to provide early warning that an organism may be in danger of being over-harvested. By the time some organisms are listed, it may be too late. At the same time, there needs to be more support to enhance the knowledge base about species and their ecosystems so that CITES monitoring and enforcement is based on sound scientific data. Unfortunately, well-intentioned, but inadequately informed policies, have sometimes held back important research.
- Consideration should be given to developing a list of species, a so-called "Green List" that are vitally important to human health, whether or not they are threatened, so that additional levels of attention and protection are in place before they become endangered.
- There also need to be efforts under the CBD process that provide adequate measures of security to source countries for organisms of biomedical interest, so that their intellectual property and benefit-sharing interests are seen to be fully protected, and concerns to the contrary do not impede access to important organisms for basic research.
- There needs to be a diversification of organisms used as biomedical research tools. This objective may simultaneously support increased awareness of the value of diverse plants, animals, and micro-organisms, and help diminish the pressure on a small number of species, particularly primates, that may already be threatened. Furthermore, an expanded effort to develop new models is likely to yield great benefits to medicine, especially in areas where viable model organisms are rare.

- Finally, more comprehensive linkages between genomic, population, geographic, and taxonomic databases need to be built, so that those in the fields of biomedical sciences and biodiversity conservation can reinforce their respective efforts aimed at promoting human health and protecting other species.

Chapter 5: Ecosytem Disturbance, Biodiversity, and Human Infectious Diseases

Key policy objective: **Ensure that all water management projects; agricultural development; exploitation of species; and forestry, mining and other extractive activities include assessments of the impacts of these disturbances on ecosystems and biodiversity, and on the resultant emergence and spread of human infectious diseases. Ensure that these enterprises take steps to minimize these impacts.**

Changes in the incidence of infectious diseases are known to accompany changes in biodiversity and ecosystem disturbances, such as deforestation, dam and irrigation systems, and agricultural development. In some of these cases, our understanding of the linkages between these changes and the pathogens, reservoirs, and vectors involved in disease transmission is well developed. For such systems, the health consequences of biodiversity loss and ecosystem disruption are relatively simple to predict, providing much information to guide policy and management decisions. In many other cases, however, the associations are circumstantial and less well understood, making generalizations and specific recommendations difficult. The better studied and understood systems, including malaria, schistosomiasis, onchocerciasis, and Lyme disease, should serve as case studies and models for other infectious diseases to guide policy-makers in their decisions about environmental management so that they are better able to protect human health.

Policy Options
- Water management projects involving construction of dams (including microdams) irrigation ponds and ditches, containers, and small impoundments should consider the effects of these practices on populations of disease vectors, particularly mosquitoes and snails, and develop adequate means of disease mitigation.
- Agricultural development should incorporate means of mitigating disease risk by avoiding the overuse of

antibiotics in livestock and poultry, preventing close spatial associations between domesticated and wild animals to prevent transmission of infectious agents between them, reducing the potential of livestock and poultry as pathogen reservoirs in the local transmission of human vector-borne diseases, and avoiding the destruction and fragmentation of natural habitat that can increase disease risk.
- Given the newly recognized beneficial role of high levels of biodiversity within vertebrate communities in reducing disease risk, human activities that erode vertebrate species diversity must be carefully considered for their epidemiological impacts. Such activities include: destruction or conversion of natural habitat, the introduction of exotic species, and the over-exploitation of native vertebrates, e.g., the consumption of "bushmeat".
- Resource extraction projects (e.g., forestry and mining) and the development of human habitations in previously undisturbed habitats must consider the potential for strongly elevating disease risk. Risk can be increased by: the creation of new habitat for disease vectors (e.g., road-building and mosquitoes), changes in vector behavior (e.g., switching to humans when alternative natural hosts become locally scarce), and the close juxtaposition of people with reservoirs and vectors of pathogens (e.g., settlements within zones of natural disease transmission among wildlife).
- Increasingly well documented linkages between climate warming and both the spatial extent and incidence of infectious diseases in humans and non-humans alike indicate that increases in disease must now be considered a consequence of greenhouse gas emissions, the primary cause of climate warming.

Chapter 6: The Role of Biodiversity in World Food Production

Key policy objectives: **Conserve and sustainably manage species and ecosystems vital for world food production—on land, in freshwater, and in the oceans.**

Policy Options
General
- Control greenhouse gas emissions
- Control air pollution over agricultural areas that leads to high ground level ozone concentrations and acid precipitation

- Control the release of gases that lead to stratospheric ozone depletion

Genetic Resources
- Expand and improve the preservation of genetic resources for crop plants and livestock.
- Coordinate database networks for genetic resources.
- Ensure fairness in rights and access.

Soil Biota
- Enhance soil fertility by organic matter enrichment.
- Apply bio-remediation to contaminated soils.

Cropping Systems
- Promote biodiversity-enhancing practices.
- Promote the use of biological controls in the context of Integrated Pest Management.
- Minimize encroachment of agriculture onto natural ecosystems.
- Retire and ameliorate marginal lands from over-cultivation and over-grazing, and restore natural vegetation wherever possible.
- Encourage farmers and agricultural districts to preserve or restore on-farm or district wetlands.
- Expand conservation reserve programs.
- Establish agro-ecosystem biodiversity reserves.

Genetic Modification of Agricultural Crops
- Institute safeguards to prevent the spread of genetically modified plants or their pollen into the open environment.
- Evaluate effects of genetically modified crops on non-target-organisms and on agro-ecosystems.
- Prevent unfair commercial exploitation of genetically modified crops.
- Investigate human health impacts of genetically-modified crops

Livestock
- Reduce over-stocking and over-grazing.
- Conserve, protect, and promote the use of a variety of domestic animal breeds.
- Regulate intensive livestock production to avoid environmental pollution.

Marine Food Chain
- Strengthen international and national control measures to prevent over-fishing, especially of vulnerable and endangered species, and other forms of marine habitat destruction.

- Prevent pollution of coastal and marine ecosystems by prohibiting the clear-cutting of forests, and by controlling agricultural run-off and sewage discharge.
- Develop ecosystem-based management of fisheries.
- Preserve ecosystems vital to fisheries such as coastal wetlands, estuaries, mangroves, coral reefs, and seagrass beds.

Mariculture
- Prevent the escape of genetically modified fish and pathogens into natural habitats.
- Regulate production to prevent environmental impacts.

Conclusions

Some over-arching policy options not covered by the chapters include:

- Establish, ideally as an extension of pre-existing national health information systems, international monitoring programs on ecosystem disruption and the resultant effects on human health. If such national health information systems do not exist, encourage their creation through developing appropriate human resources, functioning infrastructure, and effective inter-sectoral links.
- Address the implications of climate change for the linkages between biodiversity and human health under the UN Framework Convention on Climate Change (FCCC) and develop broadly-supported action plans for ensuring that they are considered together in all relevant activities that address climate change.
- Apply preventive and precautionary principles in addressing issues related to invasive alien species. Experience has shown that preventing invasions of potentially harmful species is more cost-effective than waiting until they have become established as a threat to biodiversity and human health. Sanitary, zoosanitary, and phytosanitary measures have been established, but need to be implemented more effectively. This will require that the assumptions of the World Trade Organization (WTO) on the application of these measures (the SPS Agreement) would need to be amended to place the ultimate legal burden on the proponent to show that a proposed import is safe. More broadly, the WTO should be working with the CBD and the WHO to address issues of invasive alien species that may be harmful to human health and biodiversity. At the national

level, governments will need to coordinate the activities of various agencies that are responsible for human health, animal health, plant health, transport, tourism, trade, protected areas, wildlife management, water supply, and other fields related to the issue of invasive alien species, and develop early warning systems and rapid response capacities in each country.

- Reduce production and unnecessary use of Persistent Organic Pollutants (POPs) by ensuring that national governments ratify and implement the Stockholm Convention on POPs and enforce laws concerning liability for pollution. Research has demonstrated the negative impacts on both human health and biodiversity of POPs, but such chemicals also have important advantages for human health that need to be recognized. Financial and technical support is required to reduce the reliance of developing countries on hazardous pesticides such as DDT (for malaria control). More broadly, comprehensive impact assessments need to be carried out on newly-created chemicals that may be hazardous to human and ecological health.

- Adopt an ecosystem perspective and a multi-sectoral approach to both health and biodiversity programs. All policy should be based on a sound understanding of potential systemic effects. This will require, for example, a more comprehensive approach to impact assessments. Relevant decisions under multilateral environmental agreements (MEAs) related to biodiversity need to include details of how to use ecosystem functions to improve human health, and contain information on how to implement these decisions at national and international levels.

- Strengthen environmental impact assessments carried out before development activities modify ecosystems, and require that they consider human health impacts.

- Incorporate human health issues into National Biodiversity Strategies and Action Plans (NBSAP). Under Article 6a, the CBD calls for each party to prepare a NBSAP. Most parties have done so, or are in the process of preparing them, but few have incorporated human health issues in any systematic way. Our report will provide guidance about how this can be accomplished.

- At the same time, the WHO has called on countries to develop National Environmental Health Action Plans (NEHAP) so that they can achieve environmental health and sustainable development for their citizens. As this report has demonstrated, human health ultimately depends on the health of other species and on the healthy functioning of natural ecosystems. We shall also suggest how countries can include biodiversity considerations into their NEHAPs.

It is hoped that all of the above suggested policy options will assist policy makers at the local, regional, national, and international level in their efforts to protect biodiversity and to advance human health.