

## Chapter 4

# Priorities for Global Research and Development of Interventions



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It is a profound and necessary truth that the deep things in science are not found because they are useful; they are found because it was possible to find them.

—J. Robert Oppenheimer

In R. Rhodes, *The Making of the Atomic Bomb*

### NEEDS, CONTEXT, OPPORTUNITIES, AND MAJOR CHALLENGES

Half of the entire increase in human life expectancy—a crude but easily defined measure of the health of populations—realized over recorded history occurred in the 20th century. From 1900 to 2000, life expectancy at birth increased from 48.0 to 77.1 years in the United States and from 48.0 to 77.7 years in the United Kingdom, gains of almost 30 years. However, improvements in life expectancy were not limited to the industrial nations. For example, between 1900 and 1990, life expectancy in India increased from 27 to 59 years, a gain of 32 years (Fogel 2004). These increases are largely attributable to a better understanding of biology, medicine, and public health—that is, to the benefits of research.

*Research* is traditionally defined as the generation of new knowledge and the development of new and enabling technologies to identify or respond to major gaps in current knowledge. Research includes the development of new tools, methodologies, and strategies. The World Health Organization (WHO) and its Advisory Committee on Health Research have suggested two other defining aspects of health research—namely, the verification of knowledge in different contexts and the creation and dissemination of products of knowledge. The Institute of Medicine (1997, page 1) in

the United States has defined the realm of global health research as “problems, issues, and concerns that transcend national boundaries and may best be addressed by sharing knowledge and cooperative action.”

An important corollary of this definition is that global health research is derived from individuals and institutions rather than from nation states. Thus, global health knowledge should be available to everyone, not just to the country in which it is done or that sponsored it. As a result, knowledge derived from health research is a true public good, which by definition possesses the following two special properties (Commission on Macroeconomics and Health 2001):

- *Nonexclusivity.* Thus, when supplied it does not require payment to benefit individuals or groups (for example, the benefit to the world community of eliminating smallpox).
- *Nonrivalry.* Hence, the use of the benefits by an individual, group, or country will not diminish others’ ability to benefit from the same good or service.<sup>1</sup>

Investments in research have produced remarkable improvements in global health, especially over the past 20 years. Immunization programs have led to unprecedented progress in the fight against common childhood diseases (such as measles,

pertussis, poliomyelitis, and tetanus) and in the eradication of smallpox. At the same time, vaccination programs have catalyzed the construction of a global infrastructure for epidemiological monitoring and research, especially in the Americas and in Asia. Moreover, researchers are rapidly developing many preventive, diagnostic, and therapeutic tools, and the growing power of genomics and proteomics will accelerate the pace.

The 21st century will see a continuation of the inexorable trend toward the globalization of travel, trade, and communications. At one level, economic globalization has increased disparities between countries in terms of gross domestic product per capita. On a population basis, however, economic gains by China, India, and other developing countries have made vast numbers of people substantially wealthier than ever before (Fischer 2003). Cell phones and radios are ubiquitous, even in the most remote parts of Africa and Asia, and the Internet has permitted the transmission of data across long distances rapidly,

accurately, reliably, and cheaply. With these technologies, global research relationships that once would have been impossible are now commonplace. For example, in a matter of weeks, researchers in China could sequence the gene for the surface protein of the coronavirus associated with severe acute respiratory syndrome (SARS) and then produce the surface protein as diagnostic antigen. Such speedy reaction would have been inconceivable just a decade ago.

Daunting challenges remain, however, that health research alone is unlikely to solve. The context for health is very complex and varies in different countries of the world (box 4.1). The predictable outcome of current trends is an increase in the health and technology gaps between the rich and poor countries. Tip O'Neill, the colorful speaker of the U.S. House of Representatives for 10 years, often said that "all politics is local." A provocative thesis we present here is that (a) all health care is national, and (b) all health research is global.

#### **Box 4.1**

##### **Context of Global Health**

Advances include the following:

- the globalization of knowledge and the increased mobility of the world's population
- the expansion of knowledge about disease problems in most of the developing world
- the remarkable progress achieved in the control of infectious diseases in most parts of the world
- the worldwide penetration of new forms of communication
- the promise of new technologies in biomedical research (for example, in the fields of genomics, transgenic organisms, informatics, robotics, and nanotechnology)
- the increasing flow of private resources devoted to understanding health problems related to development.

The following concerns are pertinent:

- The world's population continues to grow, numbering 6.3 billion people in 2004, with 200,000 added each day. In at least 68 countries, more than 40 percent of the population is younger than 15, whereas in wealthy countries, the proportion of elderly people in the population is expanding quickly.
- Despite falling global poverty rates, progress is uneven: 1.2 billion people still live on less than US\$1 a day, and 2.8 billion live on less than US\$2 a day. One in six children is chronically hungry.

- Disparities have increased. The richest 20 percent of the world's population now accounts for 150 times the income of the poorest 20 percent. The ratio of the income of the top 20 percent to that of the poorest 20 percent rose from 30 to 1 in 1960 to 61 to 1 in 1991 and to 78 to 1 in 1994. Evidence of global environmental degradation is apparent, especially in the developing world. For example, 45 percent of tropical rain forest has already been lost, at least 20 percent of current species will be extinct by 2030 and 50 percent by the end of the century, and half of China's and many other countries' cities already face water shortages.
- With global warming, temperatures will likely rise 1.0°C to 4.5°C this century, threatening coastal areas and changing patterns of vectorborne and epidemic disease.
- The pace of migration from rural to urban environments is speeding up, giving rise to more megacities.
- The period 1955–98 witnessed 31 civil and foreign wars, 35 million displaced people and refugees, and 127 instances of state failures—ethnic wars, revolutionary wars, and disruptive regime changes—in 96 states.
- Terrorism has become a global threat.
- Gender discrimination persists.

Sources: King and Zeng 2001, 2002; Wilson 2003; World Bank 2004; World Revolution (<http://www.worldrevolution.org>).

## Global Burden of Disease

Tables 4.1 and 4.2 summarize some of the key findings that are most relevant to a discussion of global health research priorities. The magnitude and distribution of the burden of disease across different regions in 2001 reveals a great deal about unmet research needs (Mathers and others 2003), in particular:

- Communicable diseases and maternal, perinatal, and nutritional conditions remain the major contributors to the burden of disease in Sub-Saharan Africa and in parts of East Asia and the Pacific. These regions differ significantly from all the other low- and middle-income regions and call for a unique set of priorities in relation to global health research.
- Noncommunicable diseases are already the leading contributors to the disease burden in all other low- and middle-income regions, which are undergoing rapid demographic, economic, and epidemiological transitions. Not only does the world face an epidemic of cardiovascular

disease and major unipolar depressive disorders, for example, but also these two chronic conditions already account for an increasing burden of disease and death in developing countries. Demographic changes in many low- and middle-income countries are driving the observed transition toward patterns of disease previously seen only in the industrial countries. The incidence of both ischemic heart disease and cerebrovascular disease increases rapidly with age; thus, countries in which the proportion of elderly people in the population increases will also experience increases in the relative importance of noncommunicable illness. Unlike communicable illnesses among younger people, chronic illness associated with aging cannot be entirely prevented, only delayed. These factors must be considered when setting priorities for global health research.

Children under five still account for an unnecessarily large share of the disease burden in many low- and middle-income

**Table 4.1** Broad Patterns of the Disease Burden, by World Bank Region, 2001

Category	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries	World
Population ( <i>millions</i> )	1,851	477	526	310	1,388	668	929	6,150
Communicable, maternal, perinatal, and nutritional conditions ( <i>prevalence, percent</i> )	22.2	9.4	21.8	27.1	44.3	70.4	5.7	36.7
Noncommunicable diseases ( <i>prevalence, percent</i> )	65.8	76.4	65.0	59.3	44.4	21.2	86.7	52.6
Injuries ( <i>prevalence, percent</i> )	12.0	14.3	13.2	13.7	11.4	8.4	7.5	10.7

Source: Mathers and others 2003.

**Table 4.2** Leading Causes of the Disease Burden, by World Bank Region, 2001

Rank	East Asia and the Pacific	Europe and Central Asia	Latin America and the Caribbean	Middle East and North Africa	South Asia	Sub-Saharan Africa	High-income countries
1	Cerebrovascular diseases	Ischemic heart disease	Perinatal conditions <sup>a</sup>	Ischemic heart disease	Perinatal conditions <sup>a</sup>	HIV/AIDS	Ischemic heart disease
2	Perinatal conditions <sup>a</sup>	Cerebrovascular diseases	Unipolar depressive disorders	Perinatal conditions <sup>a</sup>	Lower respiratory infections	Malaria	Cerebrovascular diseases
3	Chronic obstructive pulmonary disease	Unipolar depressive disorders	Homicide and violence	Traffic accidents	Ischemic heart disease	Lower respiratory infections	Unipolar depressive disorders
4	Ischemic heart disease	Self-inflicted injuries	Ischemic heart disease	Lower respiratory infections	Diarrheal diseases	Diarrheal diseases	Alzheimer's disease and other dementias
5	Unipolar depressive disorders	Chronic obstructive pulmonary disease	Cerebrovascular diseases	Diarrheal diseases	Unipolar depressive disorders	Perinatal conditions <sup>a</sup>	Tracheal and lung cancer

Source: Mathers and others 2003.

a. Perinatal conditions include low birthweight, birth asphyxia, and birth trauma.

regions where lower respiratory infections, diarrheal diseases, and perinatal conditions persist. Because these diseases can largely be prevented through relatively low-cost interventions, research into how best to implement these interventions and reduce the infectious disease burden in lower-income countries remains a priority.

### The 10:90 Issue

Efforts over the past two decades by the Commission on Health Research in Development, the WHO human reproduction and tropical disease research programs, the WHO Ad Hoc Committee on Research Relating to Future Intervention Options, and—more recently—the Global Forum for Health Research have been largely responsible for the increasing focus on the role of health research in economic and social development. At a time when few health research resources were being devoted to the specific health problems of developing countries, these entities played a critical role in making the case that more should be done. The Global Forum for Health Research took the most effective advocacy position, arguing that 90 percent of the US\$70 billion per year devoted to health research and development (R&D) was spent on diseases of the rich countries and only 10 percent was spent on the diseases uniquely afflicting poor countries. This advocacy has been effective and has galvanized global recognition that more research funding should be devoted to improving the health of the 85 percent of the world's population who live in developing or transition countries.

An absolute divergence in gross domestic product persists between industrial and developing countries and, thus, what they can reasonably devote to research. Infectious diseases continue to exact their highest tolls in the poorest countries, and new tools to prevent and treat HIV/AIDS, tuberculosis (TB), malaria, respiratory and diarrheal disease, SARS, influenza, and more exotic infections such as Ebola are urgently needed.

A longer-term view of global health problems recognizes the increasing convergence of health problems, particularly chronic diseases and injuries. It is no longer true that research on cardiovascular disease, diabetes, or depression, for example, is not relevant to developing countries. Vast knowledge is available on how to prevent a major portion of heart disease, lung cancer, type 2 diabetes, sexually transmitted infections, and injuries in the elderly, yet most countries do not implement that knowledge effectively. Thus, more research is needed to successfully transfer that knowledge from industrial to developing countries. For example, if monitored carefully, cost-effective, community-based antihypertensive, antiretroviral, and antidepressive treatments could have an enormous effect in most developing countries.

Increased surveillance and diagnostic capacity for emerging infectious diseases in developing countries will prevent

enormous new disease burdens in those countries, while at the same time providing early warning to industrial countries to stimulate new research on vaccines and drugs. Even though industry in developing countries may currently be devoting more effort to creating look-alike drugs, which are unlikely to add a great deal to the duration or quality of life, than to creating drugs for major global killers, and even though market incentives for interventions in resource-poor countries are lacking for most diseases, the solution is not to balkanize research and science, but to stimulate scientific capacity in all countries. Local researchers and industries in developing countries might be able to create interventions that can find a niche in markets in developing countries or that public sector or public-private partnerships are prepared to support.

### Global Health Agendas

Some major global health problems cannot be addressed with the available knowledge and existing tools. Major challenges for R&D remain to reduce the unfinished burden of infectious diseases; address the rapidly increasing burden of chronic diseases in aging populations; and reduce the unnecessary burden caused by injuries, casualties of war, and humanitarian emergencies.

**The Unfinished Agenda of Infectious Diseases.** In 1969, the U.S. surgeon general issued a now famous, if less than prescient, pronouncement: “The time has come to close the book on infectious diseases” (WHO 2000). In 2001, infectious diseases still accounted for 32 percent of the global burden of mortality and 37 percent of the global burden of disease. In Sub-Saharan Africa, they are responsible for 68 percent of deaths. The HIV/AIDS epidemic continues to spread, affecting large proportions of populations in Sub-Saharan Africa, but it is at only an early stage in Asia, when effective prevention efforts could make a difference, as they did in Thailand. AIDS is responsible for the decline in life expectancy to less than 40 years of age in five Sub-Saharan African countries. Yet recent promising results of public health efforts in Brazil, Senegal, Thailand, and Uganda demonstrate that HIV/AIDS can be prevented and controlled on a nationwide scale.

Even though the public in industrial countries often seems surprised by each new outbreak of infectious disease, the pattern of emerging infectious diseases worldwide is continuing and, at the same time, is constantly changing. Since 1970, people have been afflicted by 32 new diseases that had never previously been reported in humans, such as hepatitis C, Legionnaire's disease, Ebola, *Vibrio cholerae* 0139 epidemic, Nipah virus encephalitis, SARS, and the highly pathogenic avian influenza. The 1918 influenza epidemic killed 20 million to 40 million people worldwide. Precisely when human-to-human transmission of the avian influenza viruses will occur is impossible to predict, but it is likely to happen eventually. This

eventuality underscores the importance of encouraging systematic collaboration on emerging and reemerging infections and strengthening global surveillance and laboratory capability. A syndromic approach to diagnosis and surveillance, as for the identification of flaccid paralysis, which accelerated the elimination of poliomyelitis in the Western hemisphere, may be crucial when laboratory diagnosis is not readily available.

Finally, the deliberate dissemination of anthrax spores in September and October 2001 in the United States has raised the specter of biological terrorism, either with pathogens natural to the environment that took years to eradicate, like smallpox, or genetically engineered pathogens of unknown capability.

Thus, the global infectious disease agenda remains unfinished. Given the continuing emergence of new infectious diseases and the increasing resistance of microbial pathogens to existing drugs and of insect vectors to pesticides, as well as low compliance with treatments, it is likely to remain so.

**The Coming Epidemic: Chronic Diseases and Aging Populations.** In 1998, for the first time, chronic diseases contributed more to the global burden of disease than infectious diseases, indicating the emergence of a convergence between the principal diseases of the developing countries and the industrial countries. Worldwide, cardiovascular disease is the major cause of mortality and morbidity (13.6 percent of total disability-adjusted life years) followed by cancer (6.6 percent of total disability-adjusted life years). Diabetes type 2 is increasing in most countries of the world at an alarming rate. An unanticipated finding from the global burden of disease analysis was that psychiatric illness, particularly depression, is a major cause of disability everywhere (Murray and Lopez 1996a, 1996b). Depression is now the most important disability among women in the United States, and globally it is projected to be the second largest contributor to the burden of disease by 2020.

The success of public health and childhood immunization in reducing the number of childhood deaths from infectious disease is partially responsible for the increasing burden of chronic diseases. However, part of the increase is caused by poor eating habits, lack of exercise, smoking, and other unhealthy lifestyle choices that tend to increase with a nation's income. Even though noncommunicable diseases associated with aging are increasingly contributing to the global burden of disease, the emergence of a highly virulent infectious disease pandemic could allow communicable illnesses to reassert their primacy.

**The Unnecessary Epidemic: Injuries, Casualties of War, and Humanitarian Emergencies.** Before the analysis of the global burden of disease, the contribution of injuries to the burden of disease and disability was unclear. The most rapidly rising category of injuries is that resulting from motor vehicle crashes. If present trends continue, by 2020 motor vehicle crashes will be

the third largest contributor to the global burden of disease. Clearly public health sectors have a great deal to contribute in terms of reducing injuries from motor vehicle crashes, falls, and workplace injuries. Less amenable to intervention by public health systems will be wars and humanitarian emergencies. Obtaining accurate figures is difficult, but as Murray and others (2002) note, available statistics have greatly underestimated the burden of war and civil strife on health systems.

### **The Crisis in Health Systems**

Unprecedented advances in the development of health care technologies, drugs, vaccines, and new diagnostics, which hold the promise of healthier and longer lives for many, have profound influences on health systems worldwide; in rich and poor countries alike, they raise expectations and demand for health services along with difficult issues relating to access to information, costs, quality of care, equity, organization, and accountability. All systems are challenged by the need for quality improvement and self-learning.

The overall cost of health care has increased so much that fewer individuals can afford to pay for the best available care; thus, the financing of health systems has become central to national policy debates worldwide. Access and equity considerations pose particularly daunting challenges in poor countries, where access to treatment may be a matter of life and death for entire populations. This situation now prevails in the Sub-Saharan African countries, where the continuing spread of the HIV/AIDS epidemic has resulted in a sharp drop in life expectancy.

Comparative analysis of health systems worldwide seeks to understand the determinants of their performance—for instance, financing, human resources, health information, and quality of care—and to find ways to correct failures. Strengthening such research is one obvious way to tackle the current crisis in health systems. Another less obvious but important implication of the current situation is the need to pursue the best possible science to develop new and better tools and the concomitant need to ensure the availability and affordability of drugs and technologies where they are needed to address major health problems.

### **New Frontiers for R&D**

The extraordinary advances in science provide unprecedented opportunities for both industrial and developing regions. The following sections highlight promises as well as potential pitfalls of frontier research.

**Genomics, Molecular Epidemiology, and Preventive Medicine.** Probably the most exciting area of biomedical research for at least the next decade derives from the Human

Genome Project and other efforts to sequence entire genomes of mammals, birds, insects, and microbial pathogens. Examination of these genome sequences will allow investigators to define and understand intrinsic risks for disease as well as interactions between genes and environmental threats. The sequencing of the major microbial pathogens has given rise to molecular targets for new drugs against specific pathogens that are distinct from their host counterparts and unique antigenic fragments that may become effective components of new vaccines. Researchers have sequenced the genomes of virtually all major viral, bacterial, and parasitic infectious disease agents and placed the results in databases available to everyone, a true public good (see The Institute of Genomic Research at <http://www.tigr.org>).

The availability of these genome sequences has catalyzed ambitious research efforts. For example, a project is under way to genetically engineer the *Anopheles* mosquito to render it unable to transmit malaria. Even if this effort fails, knowledge of the mosquito's genome has given new life to medical entomology and will likely help reduce vectorborne diseases in other ways. In a second example, the growing number of available influenza virus sequences will greatly aid understanding of the epidemiology and evolution of pandemic and inter-pandemic influenza viruses and will be a powerful tool for guiding vaccine strain selection.

The genome project has already changed the understanding of health and disease (box 4.2). Until now, epidemiology has dealt largely with external and environmental risks for disease. What the Human Genome Project offers is knowledge of the other side of the health equation—that is, the intrinsic risks for disease. Previously undreamed of molecular and cellular tools to explore gene expression and function are becoming available

to provide such knowledge on a scale that was inconceivable even five years ago.

The hope is that genomics and related biomedical research on stem cells will give rise to new therapies for repairing and remodeling tissue damaged by chronic disease, from heart disease to diabetes and chronic neurological diseases. The possibility of preventive treatment has now also arisen—that is, the identification of risks for chronic disease early in life and the implementation of preventive strategies—behavioral, nutritional, or medical—to avert or overcome intrinsic risks and thereby prevent disease.

Despite the optimism and enthusiasm, a darker side of the Human Genome Project is emerging. Because individuals face different risks, the focus on “boutique medicine” will increase—that is, the focus on risks for individuals and the development of niche interventions targeting those risks, rather than the focus on populations. Identification of those intrinsic risks at birth, for example, will for some time be a luxury available to better-off children in rich countries but not to babies in poor countries or to poor populations of rich countries. Ultimately the Human Genome Project and the rapid advances in biomedical research in the industrial world have the unintended potential to increase the gap between rich and poor. If, however, most complex diseases have multigenic susceptibilities, the magic bullet approach of boutique medicine may not fulfill current expectations of rich or poor countries.

New therapies, whether they arise from genomics or from more traditional pharmacology, must be tested carefully to ensure that people in developing countries are not unfairly treated in clinical trials. Contract research organizations now carry out 60 percent of clinical trials. Many of these organizations already test products in developing countries that will

#### **Box 4.2**

##### **Uncovering Individual Risks for Specific Diseases**

Genomic information makes possible predicting individual risks for certain diseases and to certain components of the environment. One level relates to polymorphisms in individual genes that represent intrinsic risks for certain conditions (for example, breast cancer). A second level relates to differences in the expression patterns of multiple genes on DNA chips that make it possible, for example, to distinguish melanomas from lymphomas from colon cancers or stages within these cancers that no pathologist could duplicate for accuracy. Within patterns for breast cancer or certain types of leukemia, experts can now distinguish those likely to survive five years from those with

*Source:* Authors.

a poor prognosis and are creating the first generation of drugs effective against mutated genes causing specific cancers.

The promise of the genome is first and foremost a greater knowledge about disease, risks for disease, and mechanisms of pathogenesis. The exploitation of knowledge from the genome is just beginning, and practical ramifications and many effective products have yet to be realized. Despite the hyperbole about its promise, the genome does represent a new frontier, beyond random testing of compounds, for rational and evidence-based design of effective interventions.

have anticipated markets in rich countries but are unlikely, should they be licensed, to be available or affordable to populations in developing countries. This practice is both an ethical and a practical health problem.

Finally, in countries where testing for genetic risks becomes available, the likelihood of risk adjustment—that is, the exclusion of people with some risks from insurance and discrimination in relation to jobs, marriage, and housing—can be anticipated. In this information age, personal genetic information will certainly present an unprecedented challenge to privacy and confidentiality.

**A Faint Hope: Population-Based Research.** The focus of future research in the rich countries will likely be on individual risks and on interventions tailored to those risks. Yet from the point of view of the world as a whole, the most effective interventions are population-based interventions, such as vaccines, insecticide-impregnated bednets, environmental modifications, antismoking campaigns, clean water, and safe sex. With knowledge derived from biomedical science and the Human Genome Project, it is hoped that some interventions will emerge that do not require knowing any individuals' intrinsic genetic risks and that may apply to entire populations at risk. The hope is that they could be comparable to existing population-based interventions—for example, vaccines recommended for all children to prevent major infectious diseases, treatment of schoolchildren once a year with ivermectin to prevent onchocerciasis, and antismoking campaigns.

In the rich countries, research has shown that aspirin and a combination of inexpensive antihypertensive drugs reduce deaths from heart attacks by 30 percent and from strokes by 50 percent. Even though they are off patent, these interventions are currently not widely used in developing countries. These findings are the products of basic research, but their effective use will depend on operational research.

**The Next Frontier: Human Behavior and Social Determinants of Disease.** Another revolution in research is emerging: understanding the functioning of the human brain and, ultimately, human behavior. Biomarkers for neuropsychiatric disease and environmental stresses are being sought, and with MRI and positron emission tomography technology, researchers can see areas of the brain that are thinking, remembering, or enjoying music. Within the next 50 years, science will have the technical ability to begin to untangle the processes of thinking in molecular terms, with exciting or frightening possibilities to alter or affect them. Anticipating quantifiable biomarkers for stresses and psychopathology as well as objective tools for measuring the effectiveness of new psychotropic interventions in changing behavior is not unreasonable.

The factors that lead people to engage in unhealthy or destructive behaviors are more complex than simple individual choices.

Many of the lessons of social epidemiology—and the flourishing world of advertising—indicate that most behaviors, including risky or unhealthy behaviors, are socially patterned. Science has unfortunately not done a good job of learning how to change social patterns. For example, merely targeting individuals at high risk for HIV/AIDS without changing the social context that might reinforce stigmatization is not the best way to prevent disease. Indeed, in many developing countries that now provide free counseling, testing, and antiretroviral drugs for people with HIV/AIDS, the biggest barrier remains the social stigma of being HIV positive. Health systems must widen their view beyond individual patients to target entire communities and the media to change unhealthy socially patterned behavior. In the United States, epidemiological estimates indicate that 50 percent of the 2.3 million annual deaths are preventable or postponable. McGinnis and Foege (2004) find that in 2000, 19 percent of deaths were caused by tobacco, about 14 percent were attributable to poor diet and lack of exercise, and about 12 percent to injuries. One of the great challenges is to learn how to communicate what is known about the prevention of such conditions as heart disease, obesity, and diabetes more effectively.

Reliable and comparative analysis of health risks is key for preventing disease and injury. A recently published study (Ezzati and others 2003) reports estimates of the disease burden caused by the joint effect of 20 selected leading risk factors in 14 subepidemiological regions of the world. In regions where high mortality persists, four risk factors—underweight in childhood, micronutrient deficiency, indoor smoke from solid fuels, and tobacco—caused 35 to 42 percent of lower respiratory infections in 2000. In the same regions, the combined risks of high blood pressure, high cholesterol, high body mass index, low fruit and vegetable intake, and physical inactivity caused 82 to 89 percent of the burden of ischemic heart disease. Important gaps in scientific evidence about the effects of multiple risk factors and risk factor interactions persist and require further exploration (Ezzati and others 2003). In this context, investigators should not underestimate social and behavioral determinants of disease, including poverty, environment, culture, and so on.

### **“Appropriate Science” for the Developing World**

Although much discussion about “appropriate technology” for developing countries has taken place in recent decades, curiously little discussion has occurred about appropriate science. Much of the past debate assessed the imbalance of research relevant to developing countries' health problems largely as a function of the projected affordability of the products of the research—drugs, diagnostics, and new technologies developed in the industrial countries—rather than considering the potential contributions that scientists from developing countries could make both to advancing science and to addressing their

countries' health problems. Although some technologies are more or less appropriate to contexts in developing countries for reasons of cost, maintenance, or skill requirements, no limitation exists on what science or knowledge is appropriate in developing countries.

Some might argue that people in developing countries should restrict their research focus to diseases that principally affect their countries. If that were generalized to all countries, rich countries would not carry out research on tropical diseases, and the developing countries would do little research on chronic diseases. This strategy would violate two fundamental principles of science. First, connectivity in science is unpredictable: research on one disease or problem often brings conceptual or technological advances that are vital to progress in others; therefore, to the extent possible, every country should support a relatively broad spectrum of research. Second, creative science requires the freedom to pursue ideas. Progress in science is not fostered by restricting freedom of inquiry. There is every reason to believe that scientists in developing countries will create knowledge of value to diseases that primarily afflict people in industrial countries, both because of the convergence of health problems and because scientific knowledge is a public good.

Epistemology is the formal study of knowledge, and theories of how knowledge is generated abound. One such theory particularly relevant in the context of health research holds that three basic kinds of knowledge exist:<sup>2</sup>

- *Public knowledge.* This knowledge is generally published in the scientific literature, available in principle to all (with the glaring exception of those who cannot afford the major scientific journals). Because this knowledge is available to the entire global scientific community, it is a true public good. Indeed, publication in such journals is the basis for most judgments of academic and scientific achievement and is a precondition for scientific support and advancement.
- *Contextual knowledge.* This kind of knowledge is absolutely essential to bringing the fruits of public knowledge to a particular country or people. It requires learning and experience and involves cultural, social, and economic knowledge of a place, without which effectively implementing public knowledge or scientific discoveries in that context or evaluating the success of programs within national contexts is often impossible. In this case, research may have to be carried out in relation to how to implement interventions, as WHO's Special Programme for Research and Training in Tropical Diseases programs in leprosy and malaria have done in the absence of full scientific evidence. As essential as it may be, the global scientific and academic communities do not widely recognize or value contextual knowledge.
- *Tacit knowledge.* In contrast to public knowledge and contextual knowledge, tacit or intrinsic knowledge is impossible to write down or teach because it depends on a special kind

of communication between individuals that makes transmission of knowledge possible. One thinks of a few great clinical teachers who simply "know" the diagnosis without laboratory tests, or health care professionals who can put their colleagues in developing countries at ease and bring out the best in everyone being taught rather than being condescending or patronizing. Tacit knowledge is intuitive, breaks down barriers of culture or training, is highly motivating, and is often transformational in people's lives.

A few examples illustrate the importance of contextual knowledge. Many ideas and interventions are available, but knowledge on their effectiveness in different populations and on how to increase their usefulness is limited. The need to define best practices in different circumstances is urgent in relation to health. For example, data from the industrial countries indicate that providing a three-drug package containing aspirin to people with hypertension as preventive treatment might be possible on a population-based model as well as by individual physicians or medical personnel. However, Asians are more predisposed to hemorrhagic strokes than Europeans; therefore, treatment with such a regimen in Asia might have a significantly increased risk of adverse effects.

In another example, antiretroviral drugs are responsible for the 50 percent decline in mortality from HIV/AIDS in the United States, and the Global Fund to Fight AIDS, Tuberculosis, and Malaria; bilateral agencies; and the pharmaceutical industry are engaging in major efforts to make them available to resource-poor endemic countries. Despite encouraging examples in Brazil and Haiti, it is unclear whether—as in DOTS (directly observed treatment short course), a supervised method of administering drugs used for treating TB in resource-poor countries—these drugs can be given safely and effectively by community-based treatment programs, be appropriately monitored, and prevent the emergence of drug resistance or toxicity and thus provide cures for a high percentage of the patients in poor countries. However, if this method can be used, it will strengthen the fight against HIV/AIDS.

Research on community-based programs for treating children with epilepsy or adults with depression provides another example. The provision of ivermectin (Mectizan) to prevent and treat onchocerciasis revealed that even making a drug to be taken only once a year available and providing it free of charge had an almost negligible effect initially, because in some areas of Sub-Saharan Africa an effective health delivery system was simply not available. It is to Merck's credit that the Mectizan program invested considerable resources to create a delivery and monitoring system that has moved onchocerciasis to the category of diseases targeted for elimination as public health problems by WHO.

The flow of knowledge is not unidirectional. Reciprocity between research in different fields and different countries is



vital for the expansion of knowledge, and the unique contributions of developing countries to global health research are often overlooked and not always appreciated. For example, DOTS was initially developed in Tanzania, where researchers found that the best drug combination given with supervision, even though more costly, was both more effective in preventing relapse and emerging drug resistance and more cost-effective than the cheapest combinations. Similarly, artemisinin, the most rapidly acting drug for treating cerebral malaria, derives from an ancient Chinese medicine, qinghaosu, and is now a major tool in the armamentarium of malaria treatments. Research on isolated populations in developing countries can further the understanding of some of the genetic determinants of a variety of diseases, and transnational research on almost any disease has the potential to provide important insights into differences in risk factors in different contexts.

Such reciprocity depends critically on the development of scientific capacity. In terms of resource allocation, research funders often appear to have overlooked the necessary connection between research and training the next generations of researchers. Scientific and health capacity building and training are inseparable from research, yet funders seldom recognize the training aspect, and it is difficult to ensure that funding for training will be recognized as integral to research.

### **“Appropriate Technology” for the Developing World**

The development community has long debated the nature of appropriate technology for resource-poor countries. Innumerable instances exist of high-tech biomedical equipment standing unused in laboratories and hospitals throughout the developing world, serving as status symbols but not as tools to further knowledge or alleviate illness. However, the best tools appropriate for learning from the research should be made available when the primary purpose of research is to acquire knowledge, particularly if human subjects are engaged as volunteers in clinical studies to help develop that new knowledge. For example, researchers studying the effectiveness of antiretroviral drugs in resource-poor countries should have access to technology that can measure CD4 cells, viral loads, and antiviral drug resistance, which are critical for analyzing the drugs' effectiveness. Sophisticated technology may be vital to establish the scientific principle of effectiveness, thereby enabling implementation of the most cost-effective treatment program in settings where the high-tech methodology may no longer be necessary on a large scale but may remain useful for validating the effectiveness of lower-tech surrogate markers.

### **Strengthening Capacity and Institutions**

A 1996 WHO report (Ad Hoc Committee on Health Research Relating to Future Intervention Options 1996) emphasizes

three research needs that had not previously been articulated as essential to development.

- The first is a need for new knowledge through research to develop new tools for addressing continually emerging global health problems. Some of this knowledge will be generalizable, but much will be context specific and perhaps country specific.
- The second is the recognition that in many developing countries research capacity—that is, people with the training to carry out surveillance and laboratory and operational research—is limited, indicating an enormous need for training. Career structures and incentives to retain trained professionals in public health, medical sciences, and health systems in developing countries are also needed. An enormous brain drain is under way for nursing and other health professionals. The inducements to leave developing countries for higher salaries and better working conditions in the industrial world are compelling, even though many in the health field would prefer to help alleviate their own countries' health problems if it were feasible for them to do so.
- The third is that all the key priorities depend on the strengthening of institutions: universities, schools of public health and medicine, centers for disease control, and research institutions for health policy and economics. As the report indicates, remarkably few high-level institutions for research and training in public health have been created in developing countries during the past 25 years. Little progress has been made since the mid 1990s. Thus, their large needs for human capacity as well as laboratory and research infrastructure for public health are not surprising. For this situation to improve in a timely way, a new basis for cooperation in support of people and institutions must be forged between the developing and industrial countries.

Clearly governments should make greater commitments to health training and institutions. Whereas the international community has focused primarily on access to drugs in resource-poor countries, new partnerships in research are clearly needed. It is gratifying that programs that encourage and support cross-national, North-South, and South-South scientific collaborations and institutional links have been increasing, and the tremendous effect of the Bill & Melinda Gates Foundation in supporting research has emphasized the value of public and private commitments and partnerships in research. Regrettably, concomitant commitment has been lacking on the part of governments and many foundations to support training in research; career path opportunities; and institutions such as university science departments, medical schools, and schools of public health, all of which are critical for reducing the research and capacity gap between rich and poor countries.

No simple answer is available regarding the best ways to ensure effective collaboration in relation to global health. Global

### Box 4.3

#### SARS and Influenza: A Paradigm Shift for Global Research Collaboration

Outbreaks of emerging infectious diseases are by their nature unpredictable. They can be contained when they are detected early and the number of cases is small. When they are not contained, they can have enormous human and economic consequences. Economic losses attributed to SARS, which infected 8,000 people and killed 774, have been estimated at US\$30 million per day in Canada and a total of US\$16 billion to US\$30 billion in Asia.

The global response to the SARS epidemic demonstrated the power of international collaboration under leadership of WHO among public health professionals, researchers, and institutions in several countries to halt the progression of a new disease (La Montagne and others 2004). Another example is influenza: an existing international network of influenza research sites, which is critical for defining the strains to be used each year for immunization, was instrumental in developing an

unprecedented rapid response to the potentially devastating bird H5N1 influenza A.

These examples represent an important paradigm shift in global research collaboration in that they required national surveillance at the epidemiological and laboratory levels; unprecedented sharing of information at all levels of the health system; and close cooperation among clinicians, epidemiologists, and bench scientists, as well as those involved in veterinary surveillance, for the rapid development of effective intervention strategies. Integrated global responses raise difficult issues pertaining to information sharing and ownership of specimens and reagents, which have profound implications for future global health R&D. They also underscore that, despite the political temptations of denial and the economic threats of epidemic disease, honest and accurate information is essential for early warning and for making effective health policy.

*Source:* Authors.

collaborations can be difficult, they are not inexpensive, and their successes are limited in number, but they can potentially have a major effect (box 4.3). Questions arise about how to develop economies of scale in R&D and institutional capabilities; how many research centers are optimal in a developing country; how much should be done by country partners and how much in the developing countries; and what the roles of basic scientific versus epidemiological, clinical, and operational research should be. The experience of working together in true partnerships appears to be generally rewarding for scientists in both industrial and developing countries and seems to be an effective way of increasing research capacity. One set of lessons still to be learned is what the best forms of collaboration are: individual scientist, institutional, transnational, or multinational.

## PRIORITY SETTING

Setting priorities for R&D of interventions is both complex and critical in the context of severely constrained resources. A systematic approach that takes into account the disease burden as well as scientific opportunities has been proposed to guide decisions.

### Approaches

The challenge is to ensure that available resources are targeted at major health problems.

**Inherent Difficulties in Setting Priorities.** The first part of this chapter underscored the immense scope of health problems and the potential of global health research to make a difference. Given the complexity of the task and the multiple participants involved in the process, defining priorities for the global health research agenda is daunting.

Scientists tend to argue that more research is urgently needed on the diseases they are studying. Their research may certainly include worthwhile issues, but they may not be priorities in the wider context of global health R&D.

Some hold the view that the choice of priorities should begin with a statement defining topics that should not be priorities—for example, the development of vaccines (such as a leprosy or hookworm vaccine) when cost-effective treatments are available. Others strongly disagree, given the interconnectivity and unpredictability of science.

The failure of the U.S. “war on cancer” offers a useful caution on the limitations of rational planning of science. In the 1960s, a group of distinguished scientists developed a set of future research priorities for the National Cancer Program. Despite the importance of the problem, the requisite scientific knowledge was not then available to develop the modern tools that have recently been successful in treating and preventing cancer. Planning for where the new innovations and discoveries will come from is hard, and planners have to be open to changing their priorities and incorporating new approaches.

A key challenge is the problematic nature of anticipating scientific connections in advance. For example, the sequencing of a mouse leukemia virus genome as part of the National Cancer Program is what enabled scientists years later to classify HIV as a related member of the retrovirus family. Indeed, who would have predicted that research on the once arcane coronavirus would become essential to control the spread of SARS? Or that the esoteric question of whether tumor cells extinguished differentiated functions of normal body cells would lead to the discovery of monoclonal antibodies? Or that the study of sex in bacteria would give rise to the entire genetic revolution of the past half century? The need to recognize the unpredictability of science and the limitations of scientists at any time is best illustrated by Oppenheimer's statement at the beginning of this chapter.

### Systematic and Evidence-Based Approach to Priority Setting.

The process of setting priorities for the global health research agenda is complex and includes accurate or perceived assess-

ments of the burden of disease; developed countries' threat assessments, for example, in relation to bioterrorism and epidemic potential; scientific or technical opportunities; advocacy; political commitment; ethical considerations; and funding availability.

Using a systematic and evidence-based approach to priority setting, the WHO Ad Hoc Committee for Health Research Relating to Future Intervention Options (1996) undertook the first broadly based, systematic effort to formulate "best buys" for health R&D (table 4.3). The steps included assessments of the following:

- size of the disease burden
- reasons the disease burden persisted
- adequacy of the current scientific knowledge base
- cost-effectiveness of potential interventions and the probability of successful development of new tools
- adequacy of the current level of ongoing research and funding.

**Table 4.3** R&D Best Buys

Category	Key R&D investments
<i>Maternal and child health</i>	
Strategic research	Understand the relative importance, in different environments, of increased nutrient intake and of control of infectious disease as a way to reduce malnutrition
Package development and evaluation	Evaluate and refine the package for the integrated management of the sick child Develop, evaluate, and refine the mother-baby package for pregnancy, delivery, and neonatal care Evaluate the implementation of a range of family planning packages offering a wide choice of methods
New tools to improve package content	Evaluate the efficacy and optimal dosage of candidate rotavirus vaccines in low-income countries Evaluate the efficacy of optimal dosage of candidate conjugate pneumococcal vaccines and the effectiveness of existing vaccine against influenza B in low-income countries Develop and evaluate ways to increase efficiency in the Expanded Program on Immunizations by simplifying delivery and maximizing use of opportunities for immunization Evaluate the promotion of insecticide-impregnated bednets for inclusion in a future healthy household package Develop new contraceptive methods, particularly to widen the choice of long-term but reversible methods, postcoital methods for regular and emergency use, and methods for men
<i>Microbial threats</i>	
Strategic research	Screen drugs on molecular targets predicted by the genome sequence of major pathogens Investigate influences on the spread of antimicrobial resistance and approaches to monitoring resistant strains with the aim of identifying ways of slowing their emergence
Intervention development	Develop an effective prophylaxis for TB—for example, depot (or long-acting), or a vaccine chemoprophylaxis Develop a malaria vaccine Develop an HIV vaccine Develop improved methods for the diagnosis, prevention, and treatment of sexually transmitted diseases, including vaginal microbicides
<i>Noncommunicable diseases and injuries</i>	
	Establish a special program for research and training on noncommunicable diseases and healthy aging Establish a special program or initiative for research, training, and capacity building on injuries
<i>Health policy</i>	Establish a special program for research and training on health systems and policy

Source: Ad Hoc Committee on Health Research Relating to Future Intervention Options 1996.

This five-step approach has been influential. The Global Forum for Health Research and the Special Programme for Research and Training in Tropical Diseases have endorsed it and further developed it. The Global Forum's combined approach matrix links the five steps with four actors or factors determining the health status (Global Forum for Health Research 2002):

- individual, family, and community
- health ministry, health research institutions, and health systems and services
- sectors other than health
- central government macroeconomic policies.

The five steps also provide the basis for the strategic emphases matrix for tropical diseases research (Remme and others 2002).

The individual disease chapters in this volume used a slightly modified version of the framework developed by the WHO Ad Hoc Committee to identify gaps and guide the formulation of research priorities on the basis of the following premise: even though the current mix of available cost-effective interventions averts a proportion of the burden of any particular disease and the remaining burden could be further reduced with improved application of existing technologies to affected populations, a fraction of disease remains that cannot be averted. Two reasons account for this fact. First, the cost for extending the existing technology to the remainder of the population would be prohibitive. Second, the existing interventions may simply not be sufficiently effective. These two categories define the magnitude of the need for new or better tools and, in essence, serve as a rationale and indicate priorities for research.

A clear example is the case of HIV/AIDS. Neither behavioral interventions, such as exhortations for abstinence and fidelity and the provision of condoms, nor antiretroviral therapy has stopped the global spread of HIV, which challenges the scientific community to undertake more research on preventive vaccines. The availability of highly active antiretroviral therapy challenges the research community to find ways of providing effective and life-saving treatment for HIV/AIDS patients in a manner that ensures proper use and compliance, averts the development of drug resistance, and thereby becomes a financially sustainable policy.

**Participants and Decision Makers.** Two main concerns lie at the core of most discussions of the priority-setting processes: the predominance of the industrial countries and the predominance of the scientific community in formulating research agendas. Two-thirds of respondents in a survey of researchers that was funded by the National Institute of Allergy and

Infectious Diseases of the U.S. National Institutes of Health and was conducted in May 2004 were leading scientists from low- and middle-income developing countries and worked in the same region in which they held their citizenship. The survey highlighted their views about key factors influencing research priority setting as well as major barriers that hampered stronger participation by scientists from developing countries in global health research. According to the survey, the most important factors determining research priorities were the magnitude of disease burdens and the needs of the industrial countries. Major barriers to the success of research collaboration in global health were the lack of sustained funding; the difficulty of linking research, programs, and policy; the weak research leadership; and the absence of a science culture (Harley, Simonsen, and Breman 2004).

A more balanced participation of scientists from industrial and developing countries, a better gender mix, and the inclusion of major stakeholders are essential to the successful development of a truly global health research agenda. The challenge is to develop creative mechanisms for addressing current shortcomings.

The process for selecting the best research projects and programs within each priority area is well established and is grounded in scientific merit, based primarily on trust in peer review and expert judgment. Keeping this process independent from political pressures is extremely important. However, the peer review process has limitations, including a natural conservatism and risk aversion by scientists, given the responsibility for the allocation of public funding, their often narrow base of expertise in one discipline, and their specific cultural perspective. Alternative models of project selection from industry and other scientific, mission-oriented entities might offer interesting alternatives—for example, managerial systems or strategic planning processes, particularly for translating knowledge into successful interventions, an area that research is currently emphasizing.

Ethical considerations and pressures exerted by advocacy groups—such as public-private partnerships for targeted drug or vaccine development, fresh looks at “orphan drug” legislation, patent rules ensuring financial returns to industry as well as the affordability of new products in developing countries, and commitment before their development by the public and private sectors to subsidize their development or ensure markets for the products—are likely to counterbalance to some extent the lack of incentives for the pharmaceutical industry to develop drugs, diagnostics, and vaccines for which markets do not exist or are not profitable. In addition, one might hope that the growing pharmaceutical and vaccine industry in developing countries might place a higher priority on addressing nationally and regionally important health problems than do multinational companies.

The share of total R&D funds allocated to major causes of the disease burden in developing countries remains insufficient. As a result, the availability of funding to support global health R&D is ultimately the defining factor regarding the implementation of selected R&D priorities. Thus, the Bill & Melinda Gates Foundation has become a major driving force in defining priorities for global health R&D through its support of promising public-private partnerships. The new US\$200 million it provided to finance the Grand Challenges in Global Health represents the newest large influx of funds in support of global health research (see Foundation of National Institutes of Health at <http://www.grandchallengesgh.org>).

## Findings

Research agendas proposed in the various chapters fall into three broad categories:

- priorities that are already on the global health agenda
- important topics that are not yet on the global agenda, but should be pursued
- promising research topics that are not yet priorities, but should be pursued.

Michaud and others (2005) provide a more exhaustive account of the research priorities summarized here and recommended in the volume.

### **Priorities Already Part of the Global Health Agenda.**

Priorities that are already the most prominent part of the global health agenda relate almost exclusively to the unfinished agenda of infectious diseases and to the continuous threats of emerging infectious diseases, including bioterrorism. The largest investments pertain to the development of new drugs and vaccines that are needed to reduce the burden of HIV/AIDS, malaria, and TB; to the early detection and control of new highly pathogenic viral agents (for example, SARS); and to the prevention and treatment of infectious diseases resulting from microbial terrorism (for instance, anthrax and smallpox).

In 2001, the National Institute of Allergy and Infectious Diseases developed a global research plan for HIV/AIDS, malaria, and TB. The plan outlines a comprehensive approach for fighting infectious diseases that involves building a sustainable research capability domestically and internationally and enhancing global partnerships. It comprises short-, medium-, and long-term goals for research that “will lead to prevention and treatment strategies that are effective, feasible, and realistic for individual countries struggling with the burden of numerous infectious diseases” (National Institute of Allergy and Infectious Diseases 2001).

Since the mid 1970s, the WHO Special Programme for Research and Training in Tropical Diseases and a few other institutions have been key players in strengthening research and research capacity for tropical diseases that are endemic in specific developing regions—African trypanosomiasis, Chagas disease, dengue, leishmaniasis, leprosy, lymphatic filariasis, malaria, onchocerciasis, and schistosomiasis. As a result, effective control measures are now available for Chagas disease, leprosy, lymphatic filariasis, and onchocerciasis—but questions remain regarding effective implementation strategies. The other diseases still lack effective control measures and, thus, require further research to develop better tools and effective control strategies (<http://www.who.int/tdr/grants/strategic-emphases/default.htm>).

The process that led to the formulation of the Grand Challenges in Global Health represents two important departures from earlier approaches to priority setting. First, the announcement of the call for ideas in May 2003 had an unprecedented dissemination worldwide and resulted in over 1,000 submissions from scientists and institutions in 75 countries. Second, the formulation of a grand challenge, described as “a call for specific scientific or technological innovation that would remove a critical barrier to solving an important health problem in the developing world with a high likelihood of global impact and feasibility” (Varmus and others 2003) was broad and had a clear goal.

The research agendas proposed in chapters 16, 18, and 21 are extensive and encompass research on basic epidemiology and risk factors and the development of new or better drugs, vaccines, diagnostics, and intervention methods. The fact that these priorities do not represent a marked departure from previous research priorities for these conditions attests to the complexity of these diseases and their importance in the poorest countries. They will require a broadly based and sustained global research effort to overcome the rapid spread of antibiotic and insecticide resistance, limited human resources, and poorly developed health systems that severely constrain the health community’s ability to reduce the burden of disease.

### **Important Topics That Are Not Yet on the Global Research Agenda but Should Be Pursued.**

Cardiovascular diseases, neuropsychiatric disorders, obesity, diabetes, and cancers are causing a rapidly increasing share of the disease burden in all developing regions, with the exception of Sub-Saharan Africa; however, they do not yet figure prominently on the global health research agenda. The research priorities recommended independently by the authors of various chapters pertaining to major causes of noncommunicable diseases converge. Indeed, diet, lifestyle, obesity, tobacco, and alcohol are common risk factors for cardiovascular diseases, certain cancers, and

diabetes. These diseases and risk factors represent a cluster of conditions that pose similar research challenges.

The first important cross-cutting theme emerging from this cluster of chapters is the issue of portability, or how to bring knowledge and programs from one location and define how they can become best practices elsewhere. Cost-effective preventive strategies and therapeutic approaches to reduce the burden of cardiovascular diseases, cancer, diabetes, and mental disorders have been developed and tested in industrial countries. Much of the extensive knowledge base accumulated in industrial countries to prevent the development of cardiovascular diseases, diabetes, and cancers is likely to be relevant to developing countries, yet few epidemiological studies have quantified the impact of major risk factors for chronic diseases in developing regions, and few trials have been conducted to assess the effectiveness of different intervention strategies. Research to explore the transferability of cost-effective interventions from industrial to developing countries therefore figures prominently in several chapters.

The primary prevention for noncommunicable diseases in industrial countries rests on the reduction of major risk factors—namely, diet, lifestyles, and tobacco and alcohol consumption. Research priorities include the development of epidemiological databases and of intervention studies to identify cost-effective strategies to reduce the prevalence of major risk factors in different contexts in developing countries. The transfer of personal and population-based interventions to reduce the risk of cardiovascular disease, which are based on decades of research in the industrial countries, is particularly promising. Research priorities include evaluating a range of intervention strategies, from simple dietary interventions to reduce the risk of cardiovascular disease (for example, food supplementation with folic acid and linoleic acid and reduction in the salt, saturated fat, and trans fat content of processed foods), to the hypothetical “polypill,” which would combine drugs to lower cholesterol, clotting, and blood pressure. Reducing the risk of cardiovascular disease is particularly important for diabetes, which is itself an important risk factor for cardiovascular disease.

The second theme pertains to lifelong medical management of chronic conditions that cannot be cured but could be improved through the development and testing of public health prevention and treatment algorithms. This issue has been little considered in past discussions of priorities for global health research but now appears to be reasonably cost-effective. Examples include unipolar depression, bipolar disorders, schizophrenia, epilepsy, diabetes, and secondary prevention of ischemic heart disease and stroke.

The third theme pertains to crucial implementation research that combines operations research and health services and systems research. Such research is becoming central to ensuring the success of the rapid scaling-up of cost-effective interventions that is required to meet the health targets of the

Millennium Development Goals, particularly in resource-poor countries with weak health systems. In this context, further research is critical to elucidate neglected areas of health system reforms, including the following (Mills 2004):

- improving public service provision
- enhancing human resources
- ensuring accountability for health outcomes, funds, and medicines
- ensuring a functioning central government
- providing evidence for policy.

**Promising Research Topics Not Yet Global Priorities.** Other important research topics emerge from the various chapters that are not yet global priorities but that are nevertheless worthwhile pursuing. Major themes pertain to the following:

- epidemiology of injuries and cost-effective interventions to reduce the burden resulting from both intentional and unintentional injuries, particularly motor vehicle crashes and road and vehicle safety
- major risk factors for disease in different contexts (for example, tobacco, obesity, physical activity)
- medical and surgical errors
- occupational and environmental health
- risk analysis and risk communication
- delivery of care at different levels of the health system
- performance of health systems
- management of health research
- reproductive and sexual health
- health effects of global warming.

The importance of strengthening the research agenda in those and other areas and the resultant opportunities to make a real difference have not been sufficiently recognized in the past.

## KEY RECOMMENDATIONS

The priority-setting process should focus initially on defining a small number of key priorities that have a reasonable chance of succeeding and yielding cost-effective outcomes in resource-constrained environments and that are, thus, least likely to divert limited resources from being more effectively directed elsewhere. Five broad recommendations emerge from this chapter.

### Invest More Wisely in Health R&D

The focus should be on how best to invest limited resources for health R&D. This approach raises hard questions about selecting priorities and the extent to which the burden of disease and scientific opportunity to play a role. A telling example of the

dilemma may be a vaccine against bird flu. Because bird flu, A (H5N1) or other strains, is not yet a major human disease, the setting of priorities by the disease burden criterion would not accord a bird flu vaccine high priority. But knowing that between 20 to 40 million people died in the 1918 influenza epidemic, and that with a transmission time of 1.5 days, there would be few public health measures other than a vaccine that would make a difference in preventing a pandemic, developing and testing multiple candidate vaccines should be an urgent research priority.

Despite the paucity of past analysis of the relationship between the cost of research in an area and its success in improving the level of health, the amount invested is unlikely to have been the most important determinant of success. The What Works Working Group has developed 17 case studies of success stories, all of which were supported by public finance mostly in resource-constrained settings (Levine and What Works Working Group 2004). A review of lessons learned from the 20 biggest research successes in improving health in low- and middle-income countries would be a worthwhile undertaking.

### **Shift the Paradigm for Priority Setting**

The paradigm shift from dividing the world's health problems into those of the industrial countries and those of the developing countries toward creating a better understanding of the commonality of health problems between the industrial and most developing countries lies at the core of priority setting for global health research. Implicit in this shift is the recognition that the health problems of Sub-Saharan Africa are urgent and require special emphasis on the devastating burden of infectious diseases, particularly HIV/AIDS, and on the need to develop effective infrastructure for health. In time, the expectation is that the health needs of most Sub-Saharan African countries will similarly converge with those of other regions of the world and that knowledge developed in these regions will be transferable and helpful to accelerating development there.

As sociologists have long recognized, scientific and medical technology diffuses from the industrial to the developing countries, and it will, in the short term at least, increase the disparities between rich and poor countries—and perhaps to a comparable extent between the rich and the poor within countries—because more affluent and better-educated populations tend to have greater access to new technologies. However, even though disparities in health between affluent urban dwellers and poor rural populations in China and India have increased over the past decade, the overall quality of health of the entire population has increased during the same period. The hope is that information derived from research will be a great leveler over time and will contribute to reducing global inequities.

The shift in thinking in relation to the convergence of health burdens and research opportunities in both industrial and developing countries has far-reaching implications for the formulation of research priorities. In addition to emphasizing the commonality of health problems, it also emphasizes the importance of stronger global research collaboration in tackling major health problems and underscores the need for much stronger public-private partnerships to ensure that affordable drugs and vaccines will be developed and made available in resource-constrained environments.

### **Maximize the Potential of Information Technology**

No advances in science have more potential for improving health globally than the information and communication sciences. At the scientific level, the ability to handle increasingly massive amounts of data, whether from genetics, epidemiology, or clinical trials, offers the opportunity to mine the world of knowledge in ways that could not be contemplated a decade ago. Knowledge can be transferred instantaneously through the Internet; through access to open databases; and through the new public libraries of science and medicine, such as the U.S. National Library of Medicine PubMed Central. With information technology, procedures can be put in place to minimize medical and pharmaceutical errors and to provide greater accounting for medical costs and outcomes. Finally, research with partners in many parts of the world can now be carried out in real or in lag time, as in the case of clinical research on malaria (Royall and others 2004). The tools, hardware, and software for this informatics revolution must be made available as widely as possible to universities and health systems in developing countries.

### **Increase Global Research Capacity**

Research capacity continues to limit the successful implementation of those interventions most needed to improve health in resource-constrained environments. The number of people trained to carry out the surveillance and the laboratory and operational research that are so essential to the successful implementation of cost-effective interventions remains woefully inadequate. Redressing this limitation is a daunting task that will require substantial financial investment and creative approaches to create conditions that will reverse the brain drain and strengthen academic and research institutions in developing countries.

### **Create a Global Health Architecture**

Health is not the sole provenance of the health sector, and yet there is no forum or architecture for coordinating the increasingly important multisectoral interactions to improve health.

Cardiovascular and pulmonary disease in Europe and the United States are increasingly determined by China's energy sector, and global warming is impacted by the policy of the U.S. President. Health is critically affected by education, energy, transport, finance, trade, immigration, communication, and the environment. Major health problems will be most successfully addressed if partnerships can be developed between sectors, governments, NGOs, business and industry, and academe.

### Support Freedom of Scientific Inquiry

No country has a monopoly on ideas, and every country has something important to contribute to knowledge about health. The universality of science requires that scientists everywhere strive for the highest level of rigor and quality and that every country have some sustainable level of scientific research and problem-solving capacity. Encouraging and supporting scientists with the ability and passion to contribute to knowledge about health, globally or locally, must become one of the key aims of the global health and development agendas.

### ACKNOWLEDGMENT

This chapter is dedicated to the memory of John La Montagne, who was a tireless supporter of health research into problems of developing countries, a good friend, and an inspiration to us all.

### NOTES

1. Obviously, nonrivalry does not pertain to knowledge that is proprietary, as in the pharmaceutical industry, although the system of patents was created to make such enabling knowledge available to all by providing a limited monopoly for its exploitation by discoverers or inventors.

2. For this formulation, we are indebted to Suwit Wibulpolprasert, deputy permanent secretary of the Ministry of Health, Thailand.

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