Strong Medicine: Creating Incentives for Pharmaceutical Research on Neglected Diseases by Michael Kremer and Rachel Glennerster, Princeton, N.J., Princeton University Press, 2004, xiv + 153 pp.

I

HIV/AIDS, tuberculosis, and malaria are the three major killers that account for 40 percent of mortality due to infectious diseases in the world. According to *The World Health Report, 2004* (WHO), approximately 2.8, 1.6, and 1.3 million people died in 2002 respectively from AIDS, tuberculosis, and malaria. Further, a larger number of newly infected people have been added every year to the total of those living with these diseases, 5 million for HIV, from 8 to 9 million for tuberculosis, and 300 to 500 million for the malaria. What is important within the context of international development is that the majority of people infected by these diseases are concentrated in low-income countries. The burden of infectious diseases is a serious issue for many people in these countries and is considered a strong impediment to economic growth.

The purpose of the book is to provide practical ways of stimulating research and development (R&D) for neglected diseases, in particular the three major killers mentioned above. Although patients living in low-income countries sorely need medicines, they usually cannot afford them. R&D activity for these medicines does not seem to be taken seriously by pharmaceutical companies. Within these circumstances, the authors examine reasons for the lack of R&D as well as various systems designed to deal with the problems associated with R&D incentives and access to medicines. From their analysis, they conclude that a commitment to purchasing vaccines could develop. Regarding this issue, Lanjouw (2002)[1] has taken the position that since the existing patent system plays such an important role in innovations, it should be reformed in order to correspond to the actual circumstances of low-income countries. Thus, there is a difference between the two relative to whether the proposal applying to this problem is a substitute for or a complement to the existing patent system.

In the past five years, discussion of this issue has become quite meaningful. Reflecting the upsurge of international public opinion, and with the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), WTO members agreed to institute a more flexible policy regarding medicines for the three major killers from 2001 to 2003. Developing countries now have the right to produce drugs protected by the patent holder and to grant compulsory licenses to home manufacturers through this agreement. They can also import cheaper drugs from the countries that produce copies using compulsory licenses. While no country has used these rights so far,[2] these amendments heighten the bargaining

[1] Jean O. Lanjouw, "Intellectual Property and the Availability of Pharmaceuticals in Poor Countries," in *Innovation Policy and the Economy*, ed. Adam B. Jaffe, Josh Lerner, and Scott Stern, vol. 3 (Cambridge, Mass.: National Bureau of Economic Research, 2002); Lanjouw, "A Patent Policy Proposal for Global Diseases," in *Annual World Bank Conference on Development Economics, 2001/2002*, ed. Boris Pleskovic and Nicholas Stern (Washington, D.C.: World Bank, 2002).

[2] Although WTO members must give notice when invoking these rights, none of them did so until January 2005. http://www.wto.org/english/tratop_e/trips_e/public_health_e.htm.

power of low-income countries over multinational pharmaceutical companies in negotiating prices of the antiretroviral drugs and those used against tuberculosis and malaria. As a result, costs for related drugs have fallen drastically.[3]

Although the decline in prices of drugs is favorable to patients in low-income countries, it is potentially harmful to further development of medicines, therapies, and vaccines to be used against the three major killers. This is because low prices reduce the profits of pharmaceutical firms, leading to a loss in incentives for further innovation. The declining will to develop medicines for such diseases must be of concern. The problem of how to keep high incentives to develop medicines for neglected diseases and to ensure patients' access to these medicines must be more clearly addressed when prices take a downturn as a result of TRIPS amendments in the WTO. To date, no concrete plan has been developed. Hence, a book proposing a definitive system for resolving conflicts relative to R&D incentives and medicinal access has great significance.

II

The book is organized as follows. Chapter 1 guides readers in learning how serious infectious diseases are in developing countries. This is supplemented by personal experiences of one of the authors, Michael Kremer, who was infected with malaria as a youth in Kenya. He describes a situation in which most people, including his best friend, could not access medicines in the same way he could. This experience may have motivated him to take up this issue.

Chapter 2 describes differences in distributions of disease in low-income and high-income countries and also includes the status of each disease. In high-income countries, noncommunicable diseases, such as cancer and diabetes, account for approximately 80 percent of all diseases. For low-income countries diseases consist mainly of those that are infectious or otherwise communicable. Based on the idea that simple technology is appropriate for situations in which there is a weak health-care infrastructure and inadequate training of medical staff, the authors recommend vaccines as a simple tool against infectious diseases found in low-income countries. They refer to the success story of polio and smallpox in the 1980s, and the focus placed on R&D for vaccines thereafter.

Chapter 3 describes the lack of private R&D to develop drugs for low-income countries. Nevertheless, the authors point out the scientific potential for new vaccines that can come about through advances in technology. In Chapter 4, they suggest that R&D incentives for vaccines are impeded by failures both in the market and in government. Two factors affecting market failure are given: (1) "externalities" such as the consumption of vaccines by one person benefiting others due to reducing the probability of that person infecting others and (2) the "gap" between social and private returns relative to R&D investment. The presence of the former factor indicates that vaccines are public goods. Individuals can take a free ride without purchasing it. Thus, there is a market failure because private sectors will not supply such an unprofitable product. In the latter factor, the gap is increased by downward pres-

[3] The costs for treatment with antiretroviral drugs declined from around U.S.$30 per day per person in the middle of 1998 to U.S.$1 in the beginning of 2002 ("AIDS: Hope for the Best. Prepare for the Worst," *Economist*, July 13–19, 2002, pp. 65–67).

sures on prices due to the government imposing weak patent protection on developers.[4] According to the authors, this is a government failure.

Chapters 5 and 6 discuss push and pull approaches that are distinguished by the type of R&D incentive. Push programs subsidize R&D input in advance. Examples are grants and tax credits for R&D investment. Pull programs such as patent and prize systems reward developers for success in developing new products. Although push programs are necessary for basic research that is disconnected from commercial profit, they may also be an inefficient allocation of R&D input and may be susceptible to the opportunistic attitudes of developers. If there is inadequate monitoring of inventors that are funded by the government, developers may have the incentive to divert resources from original plans and exaggerate the probability of success in order to obtain more funds, thus making use of asymmetric information against the government.

On the other hand, the authors argue that pull programs encourage applied research. People who award funds to inventors do not have to monitor the researchers. This is different from push programs in that rewards are paid to developers only when a vaccine is developed. Thus, funds for developers are only spent for concrete outcomes.

While admitting the complementary nature of both push and pull programs, the authors focus on pull programs that encourage the private sector to undertake applied research. Chapter 7 includes discussion of various pull programs such as: (1) commitments to finance the purchase of products and patents, (2) provision of patent extensions on other products as a compensation for vaccine R&D, (3) establishment of best-entry research tournaments, and (4) expansion of market size. The authors propose commitment to financing the purchase of quantities of vaccine at fixed prices relative to international society.

One of the remarkable achievements of this book is discussion of vaccine pricing in Chapter 9. This includes estimations of price that are both attractive to inventors and cost-effective in saving lives. The authors propose that a range of prices between U.S.$15 and U.S.$20 per person for immunization of the first 200–250 million individuals would be acceptable to inventors and also be cost-effective. Unfortunately, pull programs suffer from a problem called "time-inconsistency." Even though governments and international organizations promised that they would give developers rewards after success in inventing vaccines, this commitment may be withdrawn under the guise of "public benefit." In order to avoid this time-inconsistency problem, both governments and international organizations must secure a credible commitment. In this way, pharmaceutical companies will not fail to undertake research. The remaining part of this chapter includes description of various institutional frameworks that may stimulate R&D to invent vaccines for diseases spreading in developing countries.

Finally, the authors advocate the necessity of making legally binding contracts for commitment to prevent the time-inconsistency problem mentioned above. The role of key sponsors, i.e., private foundations, national governments, and the World Bank, is described in

[4] In many countries, patents for medicines are waived on grounds of public health. Even at the end of the 1980s, 40 countries, including developed countries, did not admit substance patents for medicines but only process patents (Jean O. Lanjouw and Iain M. Cockburn, "New Pills for Poor People?: Empirical Evidence after GATT," *World Development* 29, no. 2 [2001], p. 265).

Chapter 12. The authors close by discussing the potential for cooperation among multiple sponsors that have reliable commitment.

III

A primary contribution of this book is its provision of concrete ways to stimulate private R&D using economic perspectives. R&D efforts for medicines that can be used against neglected disease like malaria are scarce. Private developers hesitate to exploit new drugs and vaccines for fear of making unprofitable and risky R&D investments. Although the public sector might be expected to develop provisions against such cases, the authors point out the fear that push programs will be inefficient and bureaucratic. Public and private sectors seem to have a complementary relationship as represented by Cockburn and Henderson (2000).[5] These authors described a division of labor between the two. Therefore a planned layout where only the public sector undertakes development of medicines should be dismissed and incentives for the private sector should be established.

As a precedent for public commitment, "orphan drug" legislation in the United States may be viewed. In this package, push and pull programs of subsidies, tax credits, and periods of exclusive right have already shown significant results in the last two decades. While there have been claims of applying "orphan drug" legislation to matters of slow R&D against the diseases in low-income countries, there seems to have been little concrete discussion of international application so far. This book sheds light on the possibility of purchase commitments for vaccines and strives to stimulate interest in the public, including policymakers. Further, in the context of viewing WTO amendments from 2001 to 2003 as a disincentive for private R&D, their assertion may be valid.

Purchase commitments may be real as long as fund resources and credible commitment are managed. In fact, GlaxoSmithKline, one of the greatest pharmaceutical companies, decided to develop and manufacture new vaccine for meningitis in Africa in 2003 because the World Health Organization (WHO) and Médecins Sans Frontières (MSF) announced the bulk purchase of vaccine without legal contracts. This fact may support the authors' proposal. The feasibility of such purchase commitments deserves to be examined.

The book embraces controversial issues relative to targeting diseases. The authors focus mainly on the three major killers while indicating that a similar approach could be taken to other diseases, including innovations of drugs and other medical and agricultural technologies. Although targeting diseases that kill the most people seems to be reasonable, it may be more difficult to focus on truly neglected diseases such as human African trypanosomiasis (sleeping sickness) and leishmaniasis. Such diseases may have less scale for attention and commitment. The level of motivation for R&D differs widely based on whether or not the market is secure in a given developed country and whether such disease is emerging or reemerging. Unlike the cases of malaria and tuberculosis, medicines for HIV/AIDS are supplied where an increasing number of patients in the developed world is the determinant

[5] Iain M. Cockburn and Rebecca M. Henderson, "Publicly Funded Science and the Productivity of the Pharmaceutical Industry," in *Innovation Policy and the Economy*, ed. Adam B. Jaffe, Josh Lerner, and Scott Stern, vol. 1 (Cambridge, Mass.: National Bureau of Economic Research, 2000).

of R&D efforts. In fact, Pharmaceutical Research and Manufacturers of America (PhRMA) announced that no less than 63 new medicines and 16 new vaccines against HIV/AIDS are now in development in the United States as of November 2004. Thus, treating these three diseases as equal may be inappropriate. Even if the purchase commitment should work in the case of HIV/AIDS, R&D efforts would have been directed to a strain that affected people in developed rather than developing countries. (Banri Ito)