

Fighting the Parasites of Poverty: Public Research, Private Industry, and Tropical Diseases

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Despite the immense progress made with drugs, vaccines, and simple measures of public health and cleanliness against infectious diseases in the past 100 years, these diseases still impose an intolerable burden on half of humanity. At root, the problem is the enormous maldistribution of income that leaves a fifth of the world population, a billion people, outside or barely on the margins of the world's economic market, living in absolute poverty, hardly able to scratch a living from a meager environment, and without basic measures of sanitation, clean water, or effective education. In practice, current conditions of disease transmission are those of a biblical or a medieval city, which is why we often talk of tropical diseases like leprosy as ancient.

It is the business of economics, politics, and "development" to deal with these root causes of tropical disease. But it is also the business of health workers and concerned scientists to use all their means to alleviate the suffering caused by poverty and—the greatest challenge—to achieve effective results in the face of that poverty. Despite the fact that 90% of the global disease burden occurs in the tropics, only about 5% of global health research and development (1) investment is directed to reducing that burden. Moreover, the purchasing power of the "markets" for tropical disease products is proportionally small. Those responsible for tropical disease research work within the same global financial context as those they are trying to help.

In spite of this overall bleak situation, there has been some remarkable progress in research into parasitic and tropical diseases over the last two decades. The most important factor has no doubt been the extraordinary dedication of some of the most gifted scientists in the world and the provision of some earmarked funding from private foundations and national and international research agencies and programs. This research has also been a good investment from a basic research point of view (as illustrated in this issue) through the consequent unravelling of fundamental mechanisms in biology and the immunology of infectious diseases. But the transformation

of that research through product development, to make practical, new tools to control parasites and their vectors and to reduce the burden of diseases, has raised international issues whose solution may be of even wider importance. It is these issues that I wish to address here.

In the rich world, there is a fairly sharp distinction in the responsibilities for basic research and those for product development; there, the former remain largely with the public sector and the latter with the private sector. Although the biotechnological revolution, the rise of private sector contracting in the academic world, and the consequently slow but apparently inexorable devaluation of independent academic inquiry have somewhat blurred this distinction, the operational heartland of the two types of research and their overall responsibilities have changed little. Thus, in the long run fundamental biologists can be assured that their discoveries may well one day reduce human suffering. However, in tropical diseases poverty breaks the virtuous circle that in the rich world connects research with development, development with enrichment, and enrichment with more research. National and international institutions responsible for tropical disease research have therefore increasingly realized that research is not enough—that even product development is not enough—and that they themselves must mastermind a process that covers the whole range of research and development, from basic biology to the determination of real community need (the "customer profile") to attain disease control.

Is this overambitious? Can anything really be done? There are clear examples of successful application, once a product has been developed. The eradication of smallpox and the sharp decline in poliomyelitis—with eradication in sight—are leading examples from the vaccine field. The reduction in the prevalence of leprosy, from some 12 million cases in 1981 to 2.4 million by 1993 (2), and the increase in the distribution of ivermectin—a cure for river blindness—from the drug's registration in 1987 to its reaching almost 5 million patients (and saving almost 20,000 people from blindness in 1993 alone) are good examples from the drug field. These successful appli-

cations each depended on field and operational research to determine the most effective ways of deployment. Poliomyelitis eradication would never have become feasible without a systematic search for ways of delivering active vaccines through a cold chain and, more recently, without the identification of additional ways of eliminating the wild virus from communities. With ivermectin, provided free by the manufacturer, a concerted effort with the Onchocerciasis Control Programme in West Africa (OCP) has so far spent close to \$5 million on large-scale "postregistration" studies, applied field research that showed the drug to be remarkably safe, and thus made possible the delivery of the drug with minimal medical supervision. It was also discovered that ivermectin not only prevents blindness but can improve eye lesions (3). Furthermore, simplified, low-cost approaches for rapidly mapping out the disease and delivering the drug efficiently to the most affected communities were developed.

But it is in the development part of the research and development pipeline where some of the biggest challenges for tropical disease treatments are found. Until now, pessimism has prevailed. Many have felt that product development could be driven only by a market mechanism; unless tropical diseases could provide profit margins competitive with those of other sectors of the pharmaceuticals markets, the argument went, companies would give them no serious attention. However, I believe that, on an ad hoc basis, practical solutions have now been found to overcome these problems and that these solutions can be more widely applied.

What is now required is a wider and stronger commitment to pursue these solutions in a more systematic manner. In my view, three basic commitments are required: (i) a commitment by all parties concerned to keep the costs of research and development at the lowest possible levels. This requires courage and determination by the public sector not to overregulate the private sector and investment by the public sector in the private sector on a pragmatic basis; (ii) a commitment by the private sector—some farsighted companies have shown the way forward—to undertake research and development, and production and supply, on a break-even or defined profit basis; and (iii) a commitment and willingness on all sides to establish and fund innovative and pragmatic institutional arrangements.

It is fundamental that the private sector be involved in all these commitments because private industry possesses a knowledge of pharmacologically active compounds and of the practical skills of production, management, and distribution that is almost entirely lacking in public sector

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research. Where in the world these activities are carried out is immaterial, and choices among contenders can be based on competitive bidding.

The public sector, which has been driving and seems likely to continue to drive these changes, can engage the private sector against tropical diseases in two ways: first, by identifying means for reducing development costs, and second, by promoting more appropriate analysis of the public risks and benefits of introducing new medical products. To reduce both costs and risks, we can make use of existing products and development lines where much of the toxicology or even registration is complete. For example, a satisfactory though small repertoire of drugs to treat leprosy is now available, a result of the screening of antibacterial agents already in human use. Ivermectin, a remarkably effective microfilaricide, originated from veterinary medicine. In addition, eflornithine, the so-called "resurrection drug" for African sleeping sickness, was initially developed as an anticancer drug.

Public sector-supported genome characterization of hosts and parasites will also help in identifying homologous drug targets. For example, a growth factor receptor may be a drug target for cancer and a parasite may have a homologous growth factor receptor. In addition, because host immune response appears to affect pathogenesis of most parasitic diseases, antibodies to cytokines developed for other purposes may have potential for the treatment of tropical diseases. For example, a phase III trial of antibodies to tumor necrosis factor in cerebral malaria is currently under way. Thus, product lines initially developed for profitable areas can find uses in tropical diseases.

To reduce development costs for the private sector, the public sector can support the costs of screening promising "lead" compounds against laboratory models of tropical diseases, and this screening can be done in either the private or the public sector. The private sector offers the advantage of easier access to large compound libraries, to structure-function analysis, and particularly to "hot" new compounds. Private sector screening throughput is also likely to be higher. On the other hand, an academically based screening center may be able to obtain compounds from a wider range of private companies. Both methods can work, in the appropriate circumstances: For example, compounds to treat leprosy have been successfully identified in public sector screens, and compounds active against trypanosomatids have been identified in private sector screens supported by the public sector.

There are, of course, some problems. One difficulty is to get access to compounds from hot areas of research and development, areas that are top priority for a

private company. Moreover, a compound may need chemical modification to acquire optimal activity against parasites. Both of these problems can best be handled by contractual arrangements with the private sector. Another problem is to find the means to increase the probability of success of any product development line. Because less than 10% of drugs and vaccines entering preclinical development eventually emerge as products in disease control, reductions in the risk of failure can result in major cost savings.

In contrast to earlier perceptions, in my experience the private sector will take on a product at any stage if it believes such investment will at least break even. In general, the probability of break-even increases the further a product goes along the development track. This is why public sector investment in the early steps of product development, such as drug screening, is attractive to companies. In vaccine development, where the comparative advantage of the public sector is greater than in the drug field, the public sector may have to take a product through both phase I and II trials. As an alternative or in addition to public sector support for the early stages of research and development, the public sector can also facilitate the tail end of development and product uptake. The public sector can make important contributions to clinical trials and reduce their overall costs. However, clinical trials aimed at drug registration are best supervised by the private sector: Any muddling of responsibilities at this stage may lead to delays and waste.

I have already illustrated how the public sector can play an important role in postregistration studies, but the public sector may also need to consider guaranteeing the purchase of a product once it has been developed. One way to achieve this would be to establish a dedicated fund to attract donations from several different quarters, both public and private—a means that may be particularly useful in vaccine procurement (4).

The options outlined above are not mutually exclusive and can be mixed and matched to suit a particular problem. In my view, it is unlikely that any single mechanism will be sufficient to drive product development for tropical diseases: we need a combination of methods. It is also essential to make an appropriate public risk-benefit analysis in tackling tropical diseases. There is much debate, but limited progress, in resolving issues related to standards of drug development. Discussion usually ends in a conflict between those who insist on only one global standard and those prepared to consider multiple standards.

In my view, this debate is misguided: There is only one standard. But it is not a global standard, specifying some global lev-

el of low risk, but rather in each local case the rational, and indeed political, analysis of risk against benefit. It is just such an analysis that led the government of Thailand to approve artemisinin products against malaria before they could be produced to the WHO's "good manufacturing practice" standards, because Thailand faced serious problems and growing mortality from multidrug-resistant parasites. In addition, between 1991 and 1994 Vietnam reduced malaria mortality to one-fifth of previous levels through the local production of artemisinin and its derivatives without waiting for production and testing to reach international standards. There is little doubt that these were correct risk-benefit decisions in their context. But more usually, the benefit side of the equation is underestimated, especially when the regulatory decisions are taken far away from where the health risks occur. The goal must be for risk-benefit decisions to be made as close as possible to the population at risk—and ideally by that population.

Given that in such ways we can achieve a substantial increase in commitment to drug and vaccine development for tropical diseases, there will still of course be a strong requirement for setting priorities, as resources will always be limited. The WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options was recently launched with support from the World Bank, several foundations, and several international agencies to look at global research and development priorities in health. The committee will base its work on a refined analysis of disease burden, the cost-effectiveness of current interventions (5), and the probability of success of current research and development opportunities. Thus, the committee's priorities will be based on the promise of research and development to lead to reductions in global disease burden, rather than on the places where the diseases occur. This review is timely for three reasons: First, new methodological techniques for such an analysis are being applied; second, practical experience of public-private collaboration in product development over the last decade can also be brought to bear; and third, the World Bank, one of the principal partners in the review, is making a highly commendable and active search for new financial arrangements for health. Those arrangements will certainly include relevant arrangements for research and development.

Thus, these are exciting times for international research and development in health. With such experiences gained and initiatives taken, I believe that conditions are ripe for the development of more rational and effective mechanisms to meet the need for research and development in tropical diseases. Moreover, I am optimistic that such mechanisms can be and will be

adapted for many other important areas of health-related research and development.

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Economics and the Argument for Parasitic Disease Control

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Infectious and parasitic diseases still account for well over half the total burden of morbidity and mortality in Sub-Saharan Africa, India, and much of the rest of Asia, excluding China (1). Governments of countries where these diseases are endemic face increasingly difficult choices. Economic recession coupled with depressed commodity prices has led to falling levels of real income per capita, reducing the ability of governments to raise domestic resources for public expenditure. Pressure to reduce macroeconomic imbalances and unsustainable levels of government debt has resulted in economic stabilization and adjustment policies to reduce reliance on public intervention and to encourage development of the private sector. As a result, real government health expenditure per capita declined in the 1980s in many of the countries where these diseases are the most endemic (2). This added to the burden imposed on private households which already contributed a greater proportion to total health expenditures than those in industrialized countries. There is some evidence that government health expenditures recover more quickly in countries undertaking adjustment programs, but even with recovery, resource availability will remain tightly constrained in most countries, necessitating hard choices about disease control priorities (1).

Donors, too, are facing economic constraints, and official development assistance to the health sector in developing countries stagnated in the 1980s (1). In response to these circumstances, a vigorous debate has ensued in both donor and endemic coun-

tries about the appropriate size and nature of government expenditure, the priority that should be given to the social sectors, and within the health sector, the priority that should be given to different types of programs including parasitic disease control. Three types of economic argument have been used to justify continued or increased support for parasitic disease control, and they are discussed in turn.

The Economic Cost Imposed by Parasitic Diseases

Parasitic diseases impose an economic burden on households. Scarce resources must be used to ameliorate the consequences of infection, both as direct costs—for example, for diagnosis and treatment—and as indirect costs in the form of morbidity and mortality that can reduce the time available for productive pursuits and the productivity of the time so allocated. These costs can be considerable. For example, in a group of four African case studies from an area in which average daily earnings were approximately \$0.20, these costs averaged \$9.80 (\$1.80 direct, \$8 indirect costs, 1985 U.S. dollars) per episode of malaria (3). Significant indirect costs have also been estimated for leprosy [where earnings of infected people were one-third of those of uninfected controls (4)], schistosomiasis (5), and dracunculiasis (6).

These household costs are sometimes translated into societal costs by multiplying the costs of an episode of disease by the estimated annual incidence of disease in a country. Applying this method to a set of African malaria studies (3), researchers have argued that, in 1985, malaria imposed total costs equivalent to 0.6% of the value of all goods and services produced in those countries (gross domestic product), a very substantial cost. This type of extrapolation should be interpreted carefully for a variety of reasons. For example, observed cross-

sectional differences in average earnings by disease status do not necessarily reflect the macroeconomic benefits that would result from reducing, as opposed to eliminating, a disease. In addition, research has shown the existence of coping mechanisms for disease, including the reallocation of the time of some household members to compensate for illness of other members (7). Because of this, even at the household level there may be little observable change in economic production as a result of disease, although the forced reallocation of time away from preferred uses is a clear opportunity cost to the household. Certainly, the mechanisms are far more complex than simply assuming that a duration of illness of, for example, 6 days reduces societal output by the equivalent of 6 days average productivity.

Nonetheless, studies of the relation between national economic growth rates and measures of health status of population suggest genuine costs of poor health in the form of reduced economic growth potential (1). The strength of this literature is in highlighting such costs and the fact that illness forces changes in activity patterns, thereby reducing economic potential. In addition, there is growing evidence that the economic impact of parasitic disease, particularly helminth infections, can be more subtle—retarding physical growth, development of cognitive skills, and educational participation and performance (1, 8). This reduces the longer term economic potential of individuals and, perhaps, of society: A positive and strong correlation between educational attainment and labor productivity has been demonstrated in a variety of settings (9).

The incidence of parasitic disease is greatest among the poorest people in the poorest countries. By restricting economic potential, parasitic infections exacerbate existing inequalities in society to a much greater extent than noncommunicable diseases. This is an excellent reason for intervention. However, ranking diseases strictly according to the total economic burden they place on society, as has been done for the United States (10), would not be of great value in setting priorities for parasitic disease control. It is not the size of the problem which alone should determine the priority of intervention from an economic viewpoint, but the extent to which the problem could be reduced for the available resources.

The Cost-Effectiveness of Intervention

Cost-effectiveness analysis is a powerful aid to setting intervention priorities within the health sector. Interventions can be ranked according to the size of the health improve-

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