Thirty-five thousand people die every day from AIDS, malaria, tuberculosis and other major infectious diseases, which disproportionately affect the poor in Latin America, Africa and Asia. Although patients with HIV/AIDS have benefited significantly from medical and scientific innovation over the past twenty-five years, new treatments are developed mainly in industrialised countries and for rich patients. The benefits of these life-changing medical advances have yet to filter down to poorer countries. As for the rest, few new medicines exist to tackle infectious diseases that continue to kill millions yet which in some cases are hardly known in the West.

In recent years, the focus of most research and development (R&D) funding has been on HIV, tuberculosis and malaria. There has been minimal interest in diseases such as sleeping sickness, Chagas disease and kala azar. These and other neglected diseases continue to plague millions of patients. Archaic, often toxic drugs such as arsenicals and antimonials are still used to treat these devastating diseases, even though the drugs’ active principles were identified empirically more than a century ago.

Regrettably, such diseases of poverty are ignored by the existing, profit-driven model of drug development. Of 1556 new drugs made publicly available between 1975 and 2004, only twenty were for tropical diseases and tuberculosis. Little has been done to research and develop new drugs for these diseases, as the afflicted individuals are poor and so do not constitute a viable market. However, market forces are not solely responsible for this situation: R&D of new drugs for these diseases has also been neglected by makers of public policy.

SUFFERING WITH ANTIQUATED DRUGS

The lack of products adapted for the needs of poorer countries is a pressing challenge. Today, in Africa, patients with sleeping sickness continue to be injected with a highly toxic, arsenic-based compound, just as they were fifty years ago. The drug induces so much pain that it feels like ‘fire in your veins’, and the unlucky one in every twenty treated will die from the effects of the drug itself. The choice is stark: will die without the drug, might die because of it. If this were a disease of the rich world, this level of toxicity would long ago have led to a rapid flurry of R&D to develop a less harmful treatment.
The outlook is similarly bleak for those afflicted with kala azar (visceral leishmaniasis): the treatment is another poison that has been given to patients since the 1930s. The pentavalent antimonial requires a painful hospital-based, thirty-day course of intravenous injections. Those who cannot afford this treatment die. This is the fate of many patients in the poorer parts of East Africa, eastern India, Bangladesh and Brazil, where access to healthcare is minimal.

As for Chagas disease, many patients do not even know they have it. For a Latin American child lucky enough to be diagnosed with the disease, only two drugs are available – nifurtimox or benznidazole. The more likely scenario is that it is not diagnosed and the infected individual will live for twenty to thirty years without any visible symptoms. Chagas disease gradually and irreparably damages either the heart or gastrointestinal system to the point where one day, with no warning, the individual’s heart will stop functioning.

In addition to issues of toxicity and affordability of drugs for such diseases, drug resistance is growing. Improved treatment options that include new medicines are urgently needed – options that are safe, efficient, short-course, easily administered, cheap and accessible. But who is paying heed?

**MOBILISING THE SCIENTIFIC COMMUNITY**

Basic research abounds on the molecular biology, biochemistry, cell biology, immunology and genetics of trypanosomes and leishmania parasites, the causative agents of sleeping sickness, kala azar and Chagas disease. Far more is known about these organisms than about any other parasites, and basic research continues to produce impressive insights, for example the recent decoding of their DNA. Despite all this research, however, which is regularly published in high-ranking scientific journals, almost nothing has been translated into benefits for patients, who remain neglected by the drug industry and the international research community. Much research gets no further than the publication stage, or falls through gaps at different stages of the drug development process.

The key challenges faced in the area of neglected diseases are twofold: first, how to match patients’ needs with R&D opportunities; second, how to mobilise the scientific community to pursue a needs-driven research agenda. Without commercial incentives, a more proactive and solution-oriented attitude from the international scientific community will be critical to overcoming the current neglect.

A thorough knowledge of medical and human needs, as well as of the scientific and technological opportunities available to address those needs, are necessary preconditions for optimal shaping and implementation of a needs-driven research agenda. The specific realities of patients suffering from neglected diseases must be considered. Such issues include the general health of affected populations (for example the level of malnourishment, HIV infection and/or other concurrent diseases), prevalent health infrastructures (for instance ‘treatment under a tree’, the availability of clean water, electricity and qualified health workers), availability of adequate diagnostics, cultural aspects that may influence the perception of certain types of treatment, and so on.
Once the needs are identified, mechanisms must then be developed to ensure that ‘best science’ serves as the backbone for the research agenda. And herein lies the opportunity and responsibility for the scientific community interested in these diseases to take a proactive role. ‘Best science’, focusing on innovative basic research, needs to take into account values other than the traditional assessment of producing publications that are accepted into high-ranking journals. In fact, ‘best science’ for neglected diseases should consider issues such as social benefit and public health relevance; the extent to which a project addresses the prioritised R&D agenda; inclusion of scientists from disease-endemic countries in research conception and implementation; and, last but not least, expected impact on patient needs. Creative and innovative approaches are needed to address the real problems of people suffering from neglected diseases.

In the post-genomic era of proteomics, bioinformatics, chemical genetics, pharmacogenomics and the other new life sciences, innovation is too often defined only in relation to state of the art scientific knowledge and technological achievements. However, given the enormity of the needs of patients suffering from neglected diseases, real innovation within this field will lie in the application of scientific knowledge and technological progress to the design, development and implementation of improved treatment options for these patients, thousands of whom die because of the lack of safe, effective, affordable, easy to use treatments. Innovative medical research should refer both to the means and the ends, with the primary criterion being the impact of research efforts on the morbidity and mortality of patients.

**DELIVERING CONCRETE RESULTS: DNDI’S VIRTUAL LABORATORY**

The Drugs for Neglected Diseases initiative (DNDi) is a not-for-profit organisation established in 2003 to develop new, effective and affordable treatments for neglected diseases. It was founded by Médecins Sans Frontières, Institut Pasteur, the Special Programme for Research and Training in Tropical Diseases of the World Health Organization (WHO-TDR) and public-sector research institutions from Brazil, France, India, Kenya and Malaysia. As a virtual drug development organisation, DNDi taps underused research capacity by collaborating with scientific partners from public and private sectors in both developed and developing countries.

Analysis of the current status of R&D for the trypanosomiases and leishmaniases reveals a clear shortage of projects in preclinical development. Clinical trials are mainly constituted of a cluster of new formulations of established drugs, drugs switched from other indications, or drug combinations; there is little novel in this area. To redress the balance, DNDi is taking a proactive approach to identifying new drugs and projects that have the potential to fill this preclinical gap – the aim is to develop six to eight new medicines by 2014. Already projects on nitroimidazoles, aminoquinolines and triazoles have been established to fill the immediate need. The need for new disease-specific models to improve the selection of drugs in the development phases is also recognised, and DNDi is working with partners to identify how methodologies can be improved.

In the discovery part of DNDi’s portfolio, four projects are focused on validated and well characterised drug targets, with the aim of either identifying inhibitors from compound
libraries and/or rationally designing new inhibitors of the target enzyme. DNDi also has four projects in the discovery phase on compound series with proven antiparasitic activity, with the objectives of developing more selective and drug-like compounds. In the past year DNDi has adopted another established approach in the drug discovery area, ‘compound screening’. These projects, one already well established at the Kitasato Institute in Japan and others to be established in 2006, primarily aim to identify novel chemical structures with selective activity against the parasites. Chemical diversity is an important component in the drug discovery area, different from but complementary to rational drug design. DNDi aims to ensure interaction between the two approaches and to generate novel leads for further projects.

THE COLLABORATIVE MODEL

DNDi believes that the best way to address the lack of drugs for neglected diseases is with the active involvement of regions directly affected. Therefore the aim is to develop new, field-adapted medicines for neglected diseases using and building research capacity in disease-endemic countries as well as by harnessing the significant capacity in non-endemic countries. DNDi will not only strengthen R&D capacity and infrastructure by knowledge and technology transfer, but also encourage ownership by scientists of the R&D process across regions affected by neglected diseases. Achievement of these goals will require significant investment.

The underlying principle of DNDi’s work is to promote the development of ‘public goods’ – in other words, new drugs produced through DNDi will be free of patents, thereby making medicines available for generic production. Over a hundred scientists from different private and public research organisations across the world work with DNDi, and each of the projects in its growing portfolio is collaborative. For instance, a multiregional scientific collaboration between MSF, WHO-TDR and organisations in Brazil, Malaysia, France, the UK, Burkina Faso and Thailand is working to develop two fixed dose artesunate combination therapies (ACTs) for malaria.

These collaborations are already proving successful. DNDi will make the new malarial ACTs available by the end of 2006. The two new therapies will be easier to use (just two tablets once a day for three days), less expensive than current ACTs, and available in paediatric formulations. In the case of AS/AQ (artesunate/amodiaquine), pharmaceutical company sanofi-aventis has agreed to complete development and be responsible for registration and production of the drug so that the complete treatment will be available to patients for less than a dollar for adults and fifty cents for children. A non-exclusivity clause in the agreement between DNDi and sanofi-aventis allows other manufacturers to produce the drug locally. The development of these ACTs could serve as a model for the development of future drugs for neglected diseases since, in accordance with DNDi’s principles, they are not under patent, thereby removing a significant barrier to their availability.

Two collaborative clinical trial platforms have been built in Africa, one of which will evaluate new treatment options for kala azar in East Africa, and the other for sleeping sickness.
Both will contribute to strengthening R&D capacities in the region. The cooperative effort also extends to other product development initiatives. In December 2005, DNDi entered into a collaborative agreement with the Medicines for Malaria Venture (MMV) and the University of Mississippi to further develop an antiparasitic drug that has shown promising efficacy against malaria and leishmaniasis. This collaboration requires each party to share important clinical and scientific information so as to avoid possible duplication and unnecessary spending in a field where resources are rare and precious.

ADVOCACY FOR GOVERNMENT SUPPORT

Concrete results need concrete support. DNDi believes that health is a public responsibility, and is actively canvassing governments for half its project funding. In addition to public and private foundations, individuals will be asked to provide funds for the remaining needs. However, the sooner governments share the cost of new drug development for neglected diseases and facilitate earlier adoption of these drugs, the sooner these treatments will be made available to the patients who most urgently need them.

The future holds promise, with a number of other new product development partnerships such as MMV, TB Alliance and the Institute for OneWorld Health focusing on international health problems. Yet, although some political commitments have been made in recent years, there is still heavy reliance on the generosity of philanthropists. Greater action is needed to nurture a more favourable political and regulatory environment that will stimulate and support R&D for neglected diseases. Governments alone are in a position to establish such an environment and must be made aware of and held accountable for this responsibility. While the creation of product development partnerships is an important step in neglected disease research, their work is largely driven by philanthropic organisations such as the Gates Foundation and the Rockefeller Foundation. Today, of the total of around a quarter of a billion dollars funding for product development partnerships, four-fifths comes from philanthropic donations while governments contribute a paltry sixteen per cent.5

In December 2004, DNDi began advocacy activities directed at governments across the world. A series of publications (in for example Le Monde, Global Forum Update 2005, Public Library of Science Medicine), letters to political leaders (Tony Blair, Jacques Chirac, EU commissioners, etc.), and presentations in many public arenas spearheaded these efforts. On 8 June 2005, DNDi launched an international appeal urging governments to boost innovation in neglected diseases by providing a new global framework to support needs-driven research, increased funding, access to IP protected tools, regulatory agency support, and strategies to strengthen clinical trial capacity in disease-endemic countries.

The appeal was simultaneously launched in Rio de Janeiro, Nairobi, New Delhi, Paris and London. This marked the start of a year-long campaign to gather signatures primarily from policy-makers and scientists in support of the appeal.6 These will then be presented to member states at the 2006 World Health Assembly in Geneva. The campaign serves not only to raise awareness of the issue of neglected diseases, but also to mobilise constituencies relevant to drug R&D.
CONCLUSION

It is unacceptable that in this ‘golden age’ of medical research hundreds of thousands of patients in poorer countries continue to suffer from diseases that lack modern cures. DNDi and other drug R&D initiatives committed to pragmatic and workable solutions will need political and financial support from governments to ensure that new drugs are developed and made available to neglected patients.

NOTES

6. The appeal website is at www.researchappeal.org.

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