

The manufacturing of pharmaceuticals is big business. From 1995 to 1999, the value of medicine production grew four times faster than world income <1>. Most of the world's medicines are purchased by countries like America and Japan, countries with a surplus of money and healthy, older people who take daily medicines. These people, and their purchasing power, inform global therapeutic priorities. The group of people who better represent the global burden of treatable illness, who harbor most of the world's disease and die young of infections, have the smallest amount of money. They offer poor business opportunities, and as such do not have economic authority to improve access to medicines essential to save their lives or encourage research into therapy for their relatively neglected diseases. With the exception of antibiotics, the top 10 therapeutic classes with the largest production value are targeted towards chronic illness<sup>1</sup>.

The concept of essential medicines was espoused by the World Health Assembly over over 30 years ago in an attempt to redress the widening gap between countries who had benefited from rapid pharmaceutical advancement, and developing countries who had not<sup>2</sup>. As currently defined by the World Health Organization (WHO), an essential medicine is one that “..satisf(ies) the priority health needs of a population....is efficacious,...cost-effective, and ...available in adequate amounts.” Exactly which medicines considered essential is a “national responsibility”.

It is obvious that no matter how essential a country might consider a medicine, it is often beyond their capacity to have an efficacious drug in adequate amounts. From 1975 to 1999, of 1393 new medicines that were developed, only 16 were for neglected diseases (tropical disease and tuberculosis)<sup>3</sup>. Of the remaining 1377 medicines, only two made it to the WHO's essential medicine list. All 16 of the medicines for neglected diseases did.

Chagas disease is a particularly good example of a neglected disease, and its case illustrative. It is a silent disease confined to the poorest in Latin America. Many are infected with the parasite as children, and live healthy young lives until one third of them ultimately die from its gastrointestinal or cardiac complications in middle age. It is a leading cause of congestive heart failure in Latin America<sup>4</sup>, and it is estimated that between 16 and 18 million people are infected. Several countries in Latin America have slowed transmission rates by eradicating the insect vector, but in the poorest countries, like Bolivia, the infection rate remains high<sup>5</sup>. Diagnosis is cumbersome, and unreliable. Therapeutic regimens are complex, the cure rate is poor, and the side effects so frequent in adults that therapy was, until recently, reserved for children. Despite this, there is no pediatric formulation. The effectiveness of treating chronic cases with established treatments is largely unknown<sup>6</sup>

Prevention has proved very important in controlling the disease. The Brazilian government invested 420 million dollars in Chagas disease control between 1975 and 1995, and recouped an estimated 3 billion dollars in benefit, a return of \$7.16 for each one spent<sup>7</sup>. Unfortunately, there are millions of people for whom prevention is too late,

and millions more who will get infected despite it. For these people, there is no effective therapy, and none in clinical trials. Even though their countries might cite Chagas disease treatment as a “national priority”, none will be forthcoming until it becomes a global one.

The two drugs used for therapy, benznidazole and nifurtimox, were developed decades ago. Benznidazole, first line therapy, was initially developed by Roche in 1974 during veterinary research. Production since then has been intermittent, and based on demand. This demand has come primarily from non-governmental organizations who advocate on behalf of those affected to organize “donations” or to arrange for a “subsidized” wholesale purchase. Roche is not interested in producing benznidazole any more, and is transferring its technology to a generic manufacturer in Brazil. The transfer process, thus far, has been a slow one. The company to whom the transfer is directed is facing its first experience in producing and registering drugs regarding exportation. Already they are having difficulty finding a reasonable supply of the active pharmaceutical ingredient. Millions remain dependent on Roche continuing to provide it. -The WHO has organized a donation of 250 000 tablets of nifurtimox, the second line drug, from its producer, Bayer. If there proves to be enough need, more will be purchased at a “discounted price”.

These are old drugs. Neither their scarcity nor their side effects would be tolerated by physicians in high income countries without a call for further research. The call in the case of Chagas, and so many other similar illnesses, comes from non-governmental organizations like the Pan American Health Organization, or the Drugs for Neglected Disease Initiatives, whose primary tool is advocacy, not lab work. Despite Chagas being targeted for elimination by the world health organization in 1988, progress has been slow<sup>8</sup>.

But, there has been some. In the past few years, some solutions have been developed that work through mechanisms other than advocacy, and may ultimately prove to be more tenable. In 2004, the British government announced its commitment to purchase large quantities of both a malaria and an AIDS vaccine when they are developed<sup>9</sup>. While this might sound obvious, it encourages medical research in a new way, providing an economic incentive for a skilled pharmaceutical company to research and produce a reliable product knowing that it will have someone to sell it to, lessening the uncertainty and expense of post-development marketing. Though this idea has yet to bear fruit, and has faced criticisms as overly simplistic, a similar deal could be struck for a medicine for Chagas disease. As capacity for both research and production grows in the developing world, the agreement need not necessarily be with big Pharma. And it need not be only high income countries that make the advance purchase. As the case from Brazil shows, having a healthy population is a success both ethically and economically. The difference is that providing treatment saves lives today. Prevention takes 30 years<sup>10</sup>.

Another pioneer in the field is the non-profit pharmaceutical company. OneWorld Health, one of the first, was established in 2000. An innovative model that relies on basic research and donated intellectual

property, industry expertise in drug development, and the productive capacity of the developing world, has allowed OneWorld to identify several potential compounds that might treat neglected diseases, including two for Chagas. Their work in low-income countries, from clinical trials to pill manufacturing, encourages local expertise.

For the time being, existing drugs need to be produced effectively and in appropriate quantity by their current suppliers until those who need it are able to make it, but new medicines must be sought.

Until capacity increases in the low income countries most affected by disease, wealthy countries, like Canada, can support an incentive initiative similar to Britain's. For Canada, with Bolivia as a target for Canada's International Development Agency, Chagas would be a good place to begin. Our universities must continue to support research into important, neglected fields, as they are most likely to provide innovations free from market pressure, and that can be used by organizations like One World, or DNDI. Chemical entities should be donated by industry and universities alike for testing on neglected disease. Our researchers and physicians should provide expertise and partnerships through their academic institutions as well as through established mechanisms like the UN supported Special Program for Research and Training in Tropical Disease. And medical journals, like this one, should continue to find space for research and discussion.

Our best scientists are hard at work optimizing diabetes treatments and developing safer drugs to ameliorate the pain of osteoarthritis. These are worthwhile goals. If some attention is given to developing medicines that treat infectious diseases that kill younger people, more patients will be able to enjoy their benefit.

- <sup>1</sup> The World Medicines Situation 2004. The World Health Organization. 2004. Accessed: January 17, 2006. [http://www.who.int/medicines/organization/par/World\\_Medicines\\_Situation.pdf](http://www.who.int/medicines/organization/par/World_Medicines_Situation.pdf)
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- <sup>6</sup> Reyes PA, Vallejo M Trypanocidal drugs for late stage, symptomatic Chagas disease (Trypanosoma cruzi infection). Cochr Database Sys Rev 2005 Oct 19;(4):CD004102
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