The molecular biologist against infectious disease

Infectious diseases, in both the developing and the developed world, still pose considerable challenges to biomedical research. But science alone is clearly not sufficient to overcome the burden of disease in the world

P. Helena Mäkelä

Infectious disease is one aspect of worldwide public health in which molecular biologists could bring about real change and improve the overall quality of life for many people. There are identified targets—be they viruses, bacteria or other agents—that are sufficiently different from the human body for specific intervention. And, indeed, major achievements show that this is possible: the big killers of the past—including smallpox, cholera and typhoid fever—have been eliminated from the globe, or at least from the developed world, and families do not need to worry about a newborn child dying of whooping cough, measles, scarlet fever or meningitis. However, many other infectious diseases have not disappeared, either in individuals or globally. The reasons are manifold: for some diseases the science is not straightforward, but, more frustratingly, the means by which the advances taking place through molecular biology could be implemented are not in place for other diseases.

> The excessive number of deaths and disease is part of the pathology of poverty

The diseases that still cause the greatest concern have many different profiles. There are everyday ailments, such as the common cold and other respiratory or gastrointestinal infections, which are especially common in children and continue to cause discomfort, worry, need of medical services and use of antibiotics in the developed world. The same infections are equally or even more abundant in developing countries, with the essential difference of being highly likely to cause death. Mild or even asymptomatic infections might predispose the sufferer to diseases that are not generally considered to be infectious in origin, such as gastric ulcers, many types of carcinoma, and perhaps even atherosclerosis and juvenile diabetes. In the developing world, high-profile diseases, such as HIV/AIDS, tuberculosis and malaria, are devastating in terms of the numbers of people infected and lethality, and parasitic infections, which are not deadly, but are draining of food and energy, are extremely common. Added to these existing scourges is the fact that the global spread of new diseases is now a real possibility, due to the evolutionary potential of microbes and the changes in human lifestyles and the environment that have created new niches for microbes to exploit. Finally, the deliberate spread of old or new infectious diseases through biological warfare or terrorist attacks is, as we all now know, a realistic threat.

A striking and repeated theme is that there is more disease, higher lethality and more need of medical care in the developing world. And this is the part of the world that houses 80% of its population, 90% of its children and sees 98% of all deaths in children under five years of age. When we further consider that about two-thirds of these 10 million annual deaths are due to infectious diseases (World Health Organization (WHO), 2001a; Williams *et al.*, 2002), it becomes impossible to focus our attention on the problems of the developed world alone. What is the cause of this inequality in the global disease burden? It is clearly not solely due to geography or climate, but rather to the unequal distribution of resources; the excessive number of deaths and disease is part of the pathology of poverty.

This alarming situation should spur molecular biologists into action. Research is sorely needed into the diseases that have so far not been of interest to the pharmaceutical industry because of low profit expectations, either because of the rarity of the disease or because of its prevalence in developing countries only.

> Host–pathogen interactions are the essence of disease pathogenesis: they present an exciting and feasible challenge for study with the tools we now have

Such 'orphan' diseases, including malaria, are in real need of new possibilities for treatment, and call for molecular biologists to apply their skills to their development. The problem remains that this would need public funding, not only for the laboratory work, but also for taking the product through the expensive clinical research phase, which has only recently been recognized by funding systems.

New drugs and new diagnostic methods could be designed by taking advantage of new research tools, especially the knowledge of the genome sequences of the microbes in question and of their host, humans, or, at the experimental stage, the mouse. Indeed, host–pathogen interactions are the essence of disease pathogenesis: they present an exciting and feasible challenge for their study with the tools we now have. However, this task is enormous, and so far our understanding of these interactions is only rudimentary, largely because of their complexity and diversity from microbe to microbe. But this understanding is the only safeguard that we have against new pathogens and new disease forms that the evolutionary potential of the microbial world is certain to produce in the future.

One obvious way in which molecular biologists could help in the fight against infectious diseases is to produce new antibacterial drugs, but these could be quite hard to find: current drugs have, as a rule, been found by screening natural products of soil microbes that apparently have used the weaknesses of other microbes in their struggle to survive. Industry has taken these natural products and modified them to circumvent the

defence mechanisms that pathogens have acquired, but no really new mechanisms of action have been found in recent times. At the same time, the evolutionary potential of pathogens has proved to be amazingly effective in developing resistance to antimicrobial drugs. And, with the advent of antiviral drugs, we are now seeing a corresponding evolution of antiviral resistance. Furthermore, it is not at all clear that studies of pathogenesis will provide substantial help in designing new antimicrobial agents. At best, they might suggest points of intervention applicable to one or a few organisms, but this would mean a restricted market and, consequently, a high price for the drug and the need for a specific diagnosis to be made early in the course of the disease. Neither of these problems are trivial. High costs would be prohibitive of the use of these drugs in the developing world, and would also contribute to the continuously increasing costs of medical services in the Western world. At the moment, the overwhelming majority of infectious diseases are treated without specific microbial diagnosis, partly because of a need to act rapidly and partly because of a lack of reliable diagnostic assays. Even if more rapid diagnostic methods were developed, the process of diagnosis and treatment would become more demanding, more costly and thus impossible to apply in developing countries.

Prevention of a disease wherever possible would be more effective and more appropriate than treatment. Again, infectious diseases offer an inviting research agenda for the design of preventive measures. To a molecular biologist, this first and foremost suggests vaccines. The beauty of vaccines is that they act through the powerful defence system of our bodies, the immune system, reinforcing it in selected aspects. Another beauty of vaccines is, of course, the amount of experience that attests to the feasibility and effectiveness of this approach. Increased knowledge of the pathogenesis of diseases and of the mechanisms of immunity promises new possibilities for vaccine development. Further understanding of the processes involved in stimulating the immune system is expected to allow new vaccines to be designed (Mäkelä, 2000). Ideally, these would be able to prevent several severe diseases for which there are currently no, or only unsatisfactory, vaccines: HIV, malaria and tuberculosis are the prime examples, with dengue, leishmaniasis, shigellosis and cholera following close behind. Then comes the need for vaccines for more uncommon severe infections, exemplified by group B streptococcal infections of the newborn and by group B meningococcal meningitis. Less realistic might be vaccines for groups of infections with multiple aetiologies, such as the common cold or urinary, respiratory, sexually transmitted or hospital-acquired infections in general. On the wish list for new vaccines are many further items: a higher degree of safety (although the safety requirements for new vaccines are already very strict), better stability at ambient temperatures (important in developing countries, but note that in these countries ambient temperatures can be more than 40 °C), and vaccines requiring fewer injections or no injections at all.

Most of these wishes are technically feasible. However, two big worries arise. First is the time frame: the development of a vaccine takes, at best, many years after laboratory and experimental animal research has given a clearcut proof of principle, identifying both the antigen and the required mode of administration. The subsequent clinical phases must, for safety reasons, be performed sequentially, starting from a small number of volunteers and progressing to, perhaps, tens of thousands, which is needed to demonstrate efficacy for a relatively rare infection. It must also allow time for the immune response and for the observation of the protective effect, which might need many more years. The second worry is the cost. Clinical trials that are performed as required by current codes for GCP (good clinical research practice) are very expensive. This is an important factor that affects the final price of the vaccine, which is of concern to both developing and developed countries as discussed above. The high cost of vaccine development also slows down the whole process: when no company can afford to pursue several parallel lines of investigation, they must select the one with the most potential from several candidate vaccines. As this decision will be taken on the basis of indirect data, the result might be to abandon the development of a potentially important vaccine. Escalating costs have also made vaccine development the domain of the 'big pharmaceutical' industry, in which small companies and researchers in the public sector, universities and research institutes are at present unable to participate. At the same time, vaccines with low market expectations—vaccines needed primarily in developing countries—will not be developed at all.

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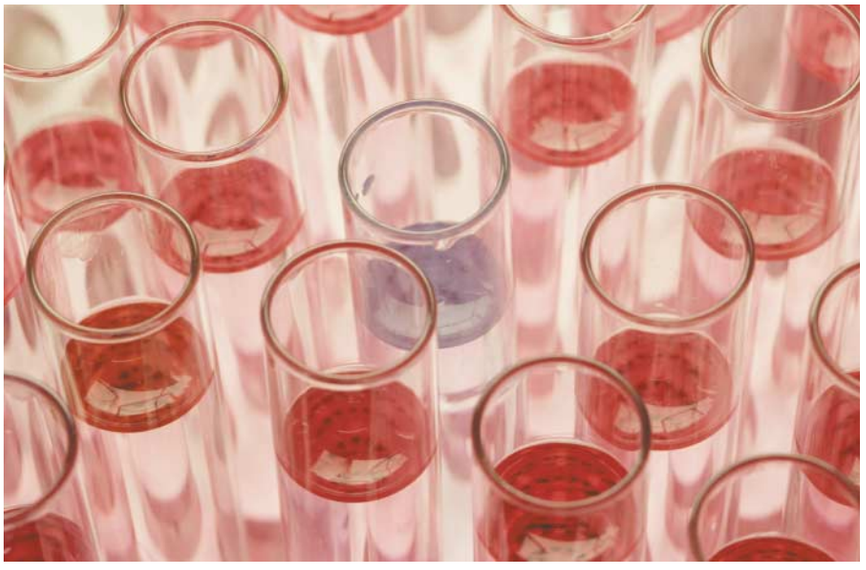
But even if molecular biology yields new drugs, diagnostic methods and vaccines, their usefulness is limited by the extent to which they can be implemented. Price is not the only factor in this. Indeed, a significant proportion of disease cases in developing countries is due to infections that could be cured or prevented without resorting to high technology. The WHO has worked for decades to improve the implementation of existing drugs and vaccines, and has created a series of simple algorithms designed to help primary health care workers to recognize, diagnose and treat common childhood diseases with very few resources. For example, for an infant with signs of acute respiratory infection (ARI) the crucial decision is whether he or she is likely to have pneumonia, and the WHO promotes an algorithm based on the child's breathing rate: if it is normal, the child does not need special medication; if it is abnormal, but the child not severely ill (diagnosed by indrawing of the chest or by blue lips), a prescription of inexpensive antimicrobials should be given. Only the few with severe pneumonia need referral to hospital for intensive care. This simple algorithm has resulted in a marked reduction in the numbers of deaths due to pneumonia, the most common killer in children (Khan *et al.*, 1990; Pandey *et al.*, 1991). Many countries have adopted these principles, but there are still major problems in their implementation. First, the mother of the child needs to decide to go to a health centre or station, which could be a long distance away. How does she know that the child is sufficiently ill to justify spending a day walking to the health centre, leaving her other children unattended and food for the family uncooked? No doubt the advice she receives in this situation varies depending on whether it comes from her husband, her mother-in-law or the local women. Then, if she goes to the health centre, how certain is it that the nurse or midwife there knows the algorithm and can apply it correctly? There could be a tendency for overdiagnosis, leading to overuse of antimicrobials, with consequent unnecessary expense and the eventual development of microbial resistance. Even if the mother is given the prescription, will the drug be available at the centre or at a nearby pharmacy? If the child needs hospital treatment, this means further expense for the family: while the mother stays in the hospital to be with the child, who will take care of the rest of the family? Does the hospital have the drugs and oxygen needed for intensive care? In the end, the likelihood of success of the ARI treatment algorithm is very slim; more likely than not, one or more links in the chain will be broken.

Prevention could be implemented more easily than treatment; again, WHO began the Expanded Programme of Immunization (EPI) 25 years ago, which has been adopted by almost all the countries in the world. It originally aimed to provide all children in their first months of life with immunization against six important diseases for which a vaccine was available at that time: TB, diphtheria, tetanus, pertussis, polio and measles. This requires a low-technology infrastructure to be implemented nationally, starting with central planning, the procurement and storage of vaccines, their distribution to the health centres at the primary health care level, ensuring a continuous 'cold chain' (meaning refrigerator temperatures for the vaccines), and the organization of vaccinations in the area. There are several key points to its success: the cold chain should not break at any point during transport or storage, vaccines should be available at health centres when the infants come to receive them, the injections must be given with sterile needles and syringes, and the families must be motivated to bring the infants for at least four visits to receive all their required doses of the vaccines.

> More health education is needed on a broad basis ranging from nutrition, illness and vaccinations of infants to sexual health; even more fundamental is teaching women to read

A global emphasis was placed on training to kick-start the EPI, and a steady improvement in vaccination rates was initially observed. After about 15 years, the worldwide coverage of the basic vaccines had reached 80% (WHO, 1999). However, progress then stopped, and coverage has not increased. Furthermore, the introduction of new vaccines that have become available since the creation of the EPI, and which are now an essential part of infant immunization programmes in the Western world, has been very slow. For example, the hepatitis B vaccine, which would have its greatest benefit in developing countries, has been available in the developed world since 1982, but was included in the EPI only 14 years later, and reached a coverage of only 30% in 2000 (WHO, 2001b). Correspondingly, the Hib vaccine (against *Haemophilus influenzae* type b) would also be of most benefit in developing countries, where it could prevent a considerable number of cases of pneumonia; although this has been available since 1990, it reached only 3% global coverage by 2000 (Peltola, 2000).



The stagnation at the 80% coverage level seems to be due mainly to local and regional differences, with some areas having very low vaccination rates because of poor infrastructure, because health is not a high priority in national politics and because resources are meagre. However, the slow introduction of new vaccines also applies to countries in which the EPI is functioning well. The low priority given to health, with inadequate knowledge of the importance of the diseases and the possibilities of their prevention, seem to be the general reasons for this. At present, a new partnership between the WHO, UNICEF, the World Bank, vaccine manufacturers, national governments and others—named GAVI, the Global Alliance for Vaccines and Immunization—focuses on addressing these shortcomings of the EPI and fulfilling the potential of immunizations. If successful, GAVI would also pave the way for the more rapid introduction of future vaccines.

How can the introduction of effective treatments be accelerated to prevent unnecessary deaths (Breiman, 2001)? At the level of the population, more health education is needed on a broad basis, ranging from nutrition, illness and vaccinations of infants to sexual health; even more fundamental is teaching women to read. At the level of primary health care, there needs to be training and retraining of staff, and the availability of basic drugs should be increased. Health systems need to be better organized, with priority at the primary care level, and epidemiological data should be collected to support planning. For national governments, health needs to be given high priority and long-term plans need to be made with a definite commitment to negotiating funding from donors. Similarly, donor organizations and governments must understand the need to support activities focusing on primary health care.

Who can make this happen? This is an important question. It points to the many different professionals who have the primary knowledge to understand what needs to be done: primary school teachers, nurses, physicians, microbiologists, epidemiologists, statisticians, administrators and politicians in developing countries should push for the action required in their particular sphere. The same professionals in Western countries would have a dual role, both to support their colleagues in developing countries with encouragement and expertise and to push for the required prioritization in their own countries and organizations. All this applies also to the molecular biologist, who is in the privileged position of knowing and understanding global needs, and is also in a position to be heard and to influence. The practical problems that need to be addressed are, admittedly, neither ones of molecular biology nor of high technology, but they need to be solved so that the discoveries and products of molecular biology can be applied for the benefit of the people that need them the most, irrespective of their geographic or economic position. Indeed, any new advances in the fight against infectious diseases are useful only to the extent to which they are applied. Removing the many obstacles to implementation is a necessary part of their development, and is thus also part of the remit of the molecular biologist.

REFERENCES

Breiman, R.F. (2001) Vaccines as tools for advancing more than public health: perspectives of a former director of the national vaccine program office. *Clin. Infect. Dis.*, **32**, 283–288.

Khan, A.J., Khan, J.A., Akbar, M. & Addiss, D.G. (1990) Acute respiratory infections in children: a case management intervention in Abbottabad District, Pakistan. *Bull. World Health Org.*, **68**, 577–585.

Mäkelä, P.H. (2000) Vaccines, coming of age after 200 years. *FEMS Microbiol. Rev.*, **24**, 9–20.

Pandey, M.R., Daulaire, N.M., Starbuck, E.S., Houston, R.M. & McPherson, K. (1991) Reduction in total under-five mortality in western Nepal through community-based antimicrobial treatment of pneumonia. *Lancet*, **338**, 993–997.

Peltola, H. (2000) Worldwide *Haemophilus influenzae* type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. *Clin. Microbiol. Rev.*, **13**, 302–317.

Williams, B.G., Gouws, E., Boschi-Pinto, C., Bryce, J. & Dye, C. (2002) Estimates of world-wide distribution of child deaths from acute respiratory infections. *Lancet Infect. Dis.*, **2**, 25–32.

WHO (1999) *The World Health Report 1999. Making a Difference.* WHO, Geneva, Switzerland.

WHO (2001a) *The World Health Report 2000. Health Systems: Improving Performance.* WHO, Geneva, Switzerland.

WHO (2001b) *WHO Vaccine-preventable Diseases: Monitory System. 2001 Global Summary.* WHO, Geneva, Switzerland.

Helena Mäkelä is at the National Public Health Institute, Mannerheimintie, Helsinki, Finland.
E-mail: helena.makela@ktl.fi

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