VIEWPOINT

ON THE BIOTECHNOLOGY REVOLUTION

SIR GUSTAV NOSSAL, MD PHD

The Biotechnology Revolution and World Health

A Five-Point Plan

Professor Nossal is Chair of the Scientific Advisory Group of Experts (SAGE) of the Global Program for Vaccines and Immunization and the Children's Vaccine Initiative of the World Health Organization, President of the Australian Academy of Science, and Professor Emeritus in the Department of Pathology, University of Melbourne.

Address correspondence to Sir Gustav Nossal, Dept. of Pathology, Univ. of Melbourne, Parkville, Victoria 3052, Australia; tel. +61 3 9344 6946; fax +61 3 9347 5242.

AT MILLENNIUM'S END, world health stands at the threshold of a major revolution. A quarter of a century into the gene cloning era, major blockbuster products for prevention, early diagnosis, and cure of diseases are now emerging in large numbers. The U.S. biotechnology companies alone have 284 candidates in clinical trial for cancer, cardiovascular diseases, infections, arthritis, neurodegenerative conditions, and many other problems. The new biology comprises not only genetic engineering technology but also amazing advances in the analysis and manipulation of protein structure and in the growth of cells outside the body.

This new biology has illuminated previously impenetrable areas such as aging, mental illnesses, nerve and spinal cord injuries, and birth defects. Though most therapeutic interventions in these areas are still well in the future, justified excitement has attracted billions of investment dollars annually in pursuit of smart ideas. In addition to biologicals such as vaccines, growth factors, hormones, and biological response modifiers, start-up companies as well as major pharmaceutical companies are coming up with tailor-made, orally active drugs based on a deep new understanding of the disease process. Triple therapy that has so transformed the outlook in HIV/AIDS is a brilliant example.

Yet the disparity between rich and poor in access to the fruits of scientific medicine remains the central dilemma of world health. Decisions about which products to develop are based on the potential for profit. The lack of financial resources cuts two ways: products whose only market is among the poorer countries (such as a transmission-blocking malaria vaccine) will not be developed, and those products that are desired by all countries (such as AIDS drugs) will initially be available only at a very high cost.

Unpalatable though it may be, some delay in the availability of new products in the poorest parts of the world seems almost inevitable. When first marketed, new products are very expensive because research and development costs are high. But there is no reason for costs to remain high forever. Large volumes, mass production technology, and competition as products come off patent will drive prices down. Hepatitis B vaccine

LIGHT SOURCES STOCK, BOSTON

now sells for about one-sixtieth of its original price.

But are we willing to accept this time lag? And even at lower prices, ability to pay may remain a serious constraint. Unless we confront the issue, the gap will widen and huge opportunities will be lost.

Let us look at the scale of the beckoning opportunity by looking first at what has already been accomplished. I have chosen my examples from the field of vaccines not only because prevention is better than cure but also because it is much cheaper. The World Bank has identified vaccines as a "best buy" both if we make more widespread use of currently available vaccines and if we invest in research and development of new and improved ones.

The power of vaccine-based strategies was proven by

"The disparity between rich and poor in access to the fruits of scientific medicine remains the central dilemma of world health."

the global eradication of smallpox in 1977. Now the World Health Organization has set its sights on the eradication of poliomyelitis. This ambitious and historic milestone will likely be achieved by the year 2000 or shortly thereafter.

Polio transmission ceased in the Western Hemisphere in 1991, and today the Americas, Europe, Australia, and many parts of Asia are polio-free. National Immunization Days (NIDs) have become an important stratagem to buttress routine infant immunization, which achieves only 80% coverage for children in developing countries. Typically, on an NID, a tremendous mobilization of political, social, media, and community effort targets all children under age five, regardless of previous immunization history, for receipt of the Sabin oral polio vaccine, often vaccinating 90% to 98% of children. Both India and China have immunized nearly 100 million children on a single day!

In China, only three cases of polio were reported in 1996, all in cross-border migrants. In India, polio incidence has also fallen dramatically. In sub-Saharan Africa, Nelson Mandela has become the symbolic head of the "Kick Polio Out of Africa" campaign and nearly all countries have conducted or plan to hold NIDs. That being said, no one pretends that the end game will be easy.

Measles eradication will be the next target. NIDs again occupy a strategic role but are a little more difficult to organize because injections rather than oral drops are required. Measles is deadly in developing countries, killing some two million children each year. Australia has recently committed itself to measles elimination. Several Caribbean, Latin American, and Scandinavian countries have eliminated domestic measles, as has the United Kingdom. Of course, until we near global eradication, a few imported cases continue to occur in these countries.

Other diseases in which real progress has been made include diphtheria, tetanus, whooping cough, hemophilus influenza B, and hepatitis B.

Altogether, immunization programs save as many as five million lives each year. Yet, 12 million children under 14, or about 10% of the birth cohort, still die annually of communicable diseases. Three-quarters succumb to diseases for which no suitable vaccine approved by regulatory authorities is available. Diarrheal diseases, acute respiratory diseases, and malaria are the three biggest killers. In older children and adults, tuberculosis causes three million deaths per year and HIV/AIDS one million and still rising.

The new biology is racing along, hoping to develop vaccines to prevent all of these diseases. Some candidates are already in clinical trial and looking good; others remain at the experimental animal stage of testing. As these products emerge from the research pipeline, how are we going to make them available in the countries that most need them? And, for the problems that have proven really tough to solve—such as malaria and HIV/AIDS—how are we to accelerate the research that will produce the big breakthroughs? I offer here, for discussion, my five-point plan for action on world health. This plan can be applied to a broad range of health issues; vaccines represent paradigmatic examples.

1. Community attitudes toward communicable diseases in the global village

Most advocates for the amelioration of endemic and epidemic communicable diseases in developing countries base their arguments on humanitarian considerations. In an increasingly selfish world, arguments appealing to self-interest should be used to buttress their case. The rich, after all, are affected by diseases of the poor. We know that HIV jumped from Central Africa to the Caribbean, from there to New York and thence to California, and soon became a pandemic of cataclysmic proportions. Multidrug-resistant tuberculosis is also everybody's problem. Moreover, a single bite from a malaria-carrying mosquito can kill a businessperson at an airport, a soldier on a peacekeeping mission, or a backpacker on a holiday. Rich countries can't stop immunizing against polio and measles until virus reservoirs in poor countries have been eliminated.

In the global village, reduction of the world burden of

infectious disease has huge spin-off benefits for rich countries whose people rarely get ill and who prize good health above virtually everything else. But the message that the new biology can deliver the goods for the developed world has been marketed poorly. It has not reached naysayers who see foreign aid as a black hole, the United Nations system as useless and corrupt, and the nongovernmental organizations as populated by impractical dreamers. Community education is important, and we must tell the story boldly—shock tactics do work.

2. A GLOBAL PARTNERSHIP FOR HEALTH RESEARCH

Health research and development that can produce new vaccines and therapeutics is a dynamic continuum: from basic biomedical or test-tube research to experimentation in laboratory animals, to applied research and development, to clinical investigation, to phased human trials. If the research phase is successful, development then demands scale-up, production technology, knowledge of the regulatory process, and eventually market research prior to making a new product widely available. Before introducing the product, we may also need sociological research on community attitudes, educational research, and an understanding of how the product works at the community level in addition to the usual studies of side effects, risks and benefits, and costs and benefits. Traditionally, the key players in this process have been academic, nonprofit institutions—chiefly universities and research institutes—along with the pharmaceutical industry.

In the era of the new biology, the biotechnology industry develops smart new products itself, blurring the lines between pure and applied research. But this reconfiguration will not solve all of our problems. First, companies find it difficult to invest research dollars to attack diseases when those who face the disease have little capacity to pay. Second, academic researchers face shrinking resources because many philanthropic foundations previously committed to tropical medicine are redeploying their funds elsewhere. Third, many of the U.N. agencies and most national foreign aid providers place research low on their lists of priorities. Finally, infrastructure for field trials, efficacy studies, and related epidemiological and social research is poorly developed in many Third World countries. A new global partnership for health research is badly needed.

In studies organized by the World Bank, the World Health Organization, and others, socioeconomic analyses of disease burden—both mortality and morbidity—have been combined with estimates of the efficacy or likely efficacy of new health interventions, creating a prioritized list of research targets. Plans are underway for an industrial research and development (R&D) consortium embracing private sector norms while seeking to develop products for the Third World. Many international health R&D programs fund capacity-building for clinical and field research in developing countries. But a great deal more "jawboning" is required on all these topics to convince decision makers that R&D pays off and holds a valid claim on aid dollars.

Development aid is often devoted to infrastructure investment intended to improve national economies. I want to promote the view that in the information age, "hard" infrastructure is becoming less important than "soft" infrastructure, including the knowledge and skill base for social, educational, and technical development. Embracing the first class scientists of developing countries in research partnerships, ensuring that they are fully involved in decision-making, and supporting improvement in the problem-solving capacity in these countries offer catalytic power that most traditional aid programs lack.

One example of this type of initiative is located not in a developing country but in a newly industrialized one. The International Vaccine Institute (IVI), for which I serve as Vice-Chairman of the Board of Trustees, was founded in Seoul, South Korea, in October 1997. An idea originally promoted by the United Nations Development Program, IVI is now a fully independent international organization, the first located in Korea, and the first public sector institute anywhere in the world devoted exclusively to vaccine research. The founders contemplate a major educational role, concentrated on capacity building in developing countries.

The Republic of Korea has provided $50 million for a new research building for IVI and will contribute 30% of the annual budget. The facility will include a pilot plant capable of making sophisticated new biologicals under good manufacturing practice conditions. (Limited capacity to make trial batches for human testing has constituted a bottleneck for academic institutions developing new vaccines.) Private industry has expressed interest in contracting with IVI for research, and the first contracts have already been signed. IVI will not duplicate the focus on basic research of existing immunology institutes and will concentrate instead on the downstream essentials, including epidemiology, clinical and field efficacy trials,

scale-up research, socioeconomic research, and health policy research.

IVI marks a transition for Korea from being a recipient to a dispenser of aid, a signal achievement.

3. A NEW VISION OF PUBLIC SECTOR-PRIVATE SECTOR INTERACTION

While there are still public sector vaccine manufacturers in a few countries, the vaccine industry is now overwhelmingly concentrated within the private sector. Not so long ago, many academics and humanitarians viewed vaccine companies as adversaries, and vice versa. The 1980s' global mobilization for childhood immunization demonstrated that collaboration is possible. I believe that a full partnership, with mutual respect, is truly achievable.

The United Nations Children's Fund (UNICEF) has purchased massive quantities of vaccine for global immunization efforts. Vaccine companies have responded competitively with low prices. Today hundreds of millions of doses are acquired annually. These contracts, under which a single dose is very cheap, represent significant production and sizable income to the manufacturers. Unbelievable though it may seem, a single dose of Sabin polio purchased by UNICEF in a large quantity now costs only eight U.S. cents. The six most commonly used vaccines together cost only $1 per fully immunized toddler. Of course, the newer, smarter vaccines will be more expensive, but even for new products, competition can and is driving prices down.

A tiered pricing system and assured high volume purchases will be key factors in making vaccines available in poorer countries. Countries can be classified into tiers based on population and income per capita. For the poorer and smaller, more outside help will be required. If companies can recoup their research and development costs in richer countries, where the price of vaccines is less of an inhibiting factor, they can offer vaccines to the poorer countries at just above the marginal cost of production. Every dose sold will still contribute to their overall return on investment. If the volume is large and assured for several years, companies will perceive smaller risks when investing in the new plants that are required in order to increase output. Optimal results require industry to become a full partner in the process, trusted and valued and included in planning and priority setting.

Industry representatives now occupy respected seats at the table and make a strong contribution to the Children's Vaccine Initiative. Industry participates in research and strategy meetings of my program within WHO, the Global Program for Vaccines and Immunization. This dialogue must be expanded, and older prejudices must be set aside.

4. NEW PATTERNS OF RESOURCE MOBILIZATION

No matter how volumes rise and margins are shaved, the global vaccination campaigns required for final disease eradication will be expensive. Yet today's resources are already under great strain. Overseas aid or development assistance will continue to be an important element. But development assistance budgets are shrinking all over the world as politicians excuse national selfishness on the pretext of great waste and corruption in recipient programs—which is indeed sometimes a problem. The U.N. target of 0.7% of GDP is honored by only a handful of European countries. Unrealistically and without much hope, I plead for a reversal of this trend. Regretfully, there are few votes to be garnered by supporting development aid.

To make matters worse, multilateral aid that pools money for organizations such as UNICEF and WHO that are often seen as inefficient and corrupt is the least politically palatable investment. Bilateral aid, from one country to another, is more attractive because it supports certain national trade and foreign affairs objectives. It is my earnest hope that when poliomyelitis is finally eradicated from the world, the triumph will have a galvanizing effect on world opinion and will show what else is possible through the multilateral approach.

Due to the decreases in development aid, low-interest loans have a big role to play. The World Bank and regional development banks increasingly see health as a good investment and have begun modest loans for vaccination programs. The World Bank has ranked immunization as one of the most cost-effective health interventions, measured in disability-adjusted life-years saved per dollar spent. I see real merit in a revolving fund in which loans are repaid as nations reach greater affluence—in part because of the better health and social conditions of their citizens—and these returning funds are made available to countries not as far along the development pathway.

Finally, resources will need to be mobilized within developing countries themselves, aided by a growing awareness that children really need not die. In many developing countries, health has not been a high priority,

partly because no one believed that health was achievable through efficient investments such as vaccines. Even today, too few leaders understand how much can be achieved with current resources. Countries where Coca-Cola sales are high and no one lacks a transistor radio, reflecting rising per capita income, still say they cannot afford the hepatitis B vaccine. This deprives their children of protection from the first anti-cancer vaccine in history (hepatitis B being the most common cause of liver cancer). Community education and advocacy targeted at decision makers is required here.

Philanthropy also has a role. Rotary International, with its brilliantly successful Polio Plus campaign, has shown what the philanthropic sector can do. I am repeatedly stunned by the more than $500 million that Rotary has brought to the vaccine party quite apart from its volunteer work on the ground, particularly on National Immunization Days. Rotary's example is a shining light for others to follow, but to Rotarians themselves I say: please hang in there until polio eradication is completed!

5. SENSIBLE MEANS OF TECHNOLOGY TRANSFER

A difficult dilemma remains. How much should we rely on the manufacturing might of industrialized countries and how much should we encourage vaccine production in developing countries themselves? A single industrial-world producer of a new vaccine, if guaranteed sales of half a billion doses per year for several years, could produce that vaccine at lower cost per dose than a small Third World manufacturer. I don't believe in an "either-or" resolution, but in a sensible balance and compromise. No doubt some small developing country manufacturers, unable to meet international quality control standards, should quietly shut. Equally, there is little doubt that investment, training, and goodwill on the part of management can bring about first class manufacturing capability in developing countries, as at Bio Farma in Bandung, Indonesia.

Opportunities for technology transfer will arise, but given the trend toward concentration within the pharmaceutical industry, there will not be room for very many players. There is simply no need for a plant in every country, and only a certain number of countries should aspire to independent capability. There is room, however, for joint ventures and other forms of partnership between multinational firms and new enterprises in developing countries. I favor a pluralistic array of solutions and a light guiding hand—different patterns being suitable for different countries.

There must however, be universal respect for intellectual property rights as technology transfer proceeds. Without this central plank of international trade, we will destroy the fledgling partnerships that have been carefully built. Such cooperation has already engendered a new attitude within industry toward health in developing countries. The watchword here is move forward, but with caution and common sense.

CONCLUSIONS

As the new millennium approaches, the world presents some startling contrasts. On the one hand, I sense a certain democracy fatigue. People have lost faith in politicians and are perturbed about intractable problems such as unemployment, the environment, violence, drugs, and alienation of underclasses. On the other hand, a largely deregulated world without borders, freed from the threat of nuclear annihilation and multicultural to a degree never contemplated—a true global village—beckons with untold possibilities. The end of colonialism, the emergence of independence and national pride, and rapid economic development of a dozen or more newly successful countries represent defining achievements of the 20th century. Yet, this world, so successful in many respects, has failed to alleviate the problem of poverty, leaving a third of humanity bereft of a real chance to contribute to the great adventure.

Education and health are the two great keys. We must use all public sector institutions, flawed though they may be, to close the gap between rich and poor. We must work with the political sector to convincingly paint the breadth and depth of the problem and the size of the opportunity as well. We must inspire the young, many of them so able, so well trained, and still so idealistic. We must glory in true partnerships between developed and developing countries. Our experience richly demonstrates that human ability knows no national boundaries. Above all, we must not abandon the hope of progress. I close with some words from one of the great biologists and thinkers of the century, Sir Peter Medawar: "To deride the hope of progress is the ultimate fatuity, the last word in poverty of spirit and meanness of mind."

This article was adapted from a presentation at the Center for Australian and New Zealand Studies, Georgetown University, Washington DC, October 23, 1997. ■