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**EARLY INTERVENTION - NEW VACCINES:
POLICY**

D.A. HENDERSON, M.D., M.P.H.

Associate Director for Life Sciences

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The challenges and potential for all manner of new vaccines has been eloquently described by Dr. Ada. The magnificent foundation laid by contemporary advances in biomedical science and the array of tools already provided us by biotechnology now make it possible to dream the impossible. One such dream is a "children's vaccine"--one or two multivalent preparations to be given by mouth at or soon after birth which will protect a child throughout his lifetime against 20 or more diseases. Another dream is a safe and effective fertility vaccine to which Dr. Ada has alluded. And, high on everyone's priority list are vaccines to protect against HIV and malaria. It is apparent from careful examination of the state of knowledge with respect to each of these challenges -- what is known, what problems must still be overcome -- that many, if not most, of these objectives could be achieved by the end of the decade without postulating landmark scientific breakthroughs.

Clearly, we are on the threshold of a new era in prevention and public health albeit resources and a dedicated research effort will be needed. I would be remiss, however, in failing to note that there are some who disagree, who disparage developments in the vaccine field as "technological fixes," who argue that all resources should be used in wider application of the interventions already in hand. Had such individuals been responsible for dispensing polio funds in the 1950s, hospitals throughout the world would now be well-equipped with Drinker respirators and the wheelchair industry would be far more prosperous than it is.

Prevention of disease through immunization has been demonstrated time and again to be, by far, the most cost beneficial procedure in our entire medical armamentarium -- and one of the simplest to perform. Despite this, it has remained, until recently, a neglected orphan in health care delivery and on research agendas. Sickness care has had first call on resources and first priority in health care delivery -- however, this situation has begun to change. It has become apparent that ever escalating investments in sickness care are bringing only marginal improvements in health and well-being. The words "vaccination" and "prevention" are, at last, beginning to assume more appropriate status.

Suppose new vaccines became available, could they be utilized effectively? Most are surprised to learn that there is now in existence a global system for providing vaccines to children. The network operates sufficiently well so that more than 80% of the world's 140 million infants are now being vaccinated annually against measles, polio, diphtheria, tetanus, pertussis and tuberculosis. This is a global initiative which has come to fruition over the past decade. It operates under the banner of the Child Survival Program, a program supported primarily by WHO, UNICEF, Rotary International and the Rockefeller Foundation as well as national development agencies such as our own AID. By any standard, it is the most comprehensive, organized social service network ever established. An estimated 2.5 million deaths are being averted each year and in the Western hemisphere poliomyelitis is on the verge of eradication. The last known case occurred more than 8 months ago.

The scenario for the future would appear to be very bright indeed. With a now well established delivery system in place and with a cornucopia of new products on the horizon, a veritable revolution in improved health for hundreds of millions of people would appear to be in store.

Regrettably, this is not the case and herein lies the great challenge for this decade. The reasons are several, as I shall enumerate, but, as yet, the obstacles are great, the solutions are not clear and the answers will not be simple. The genesis of the problem rests with the very history and nature of immunization itself, with the manner in which vaccines have traditionally been developed and produced and with the manner in which immunization programs have traditionally been funded.

Since Jenner's day, when the first vaccine became available, the provision of immunization has been generally accepted as a community responsibility. From the beginning, public vaccinators were appointed and paid by government bodies. They also assumed responsibility for vaccine purchase and supply. Where vaccination was also offered by private practitioners, public programs provided for those who could not pay. Even today, throughout most of the world, vaccination is publicly funded and, indeed, it is the only practical approach in developing countries in particular where large scale community-based programs are conducted.

Public funding has both advantages and disadvantages. It permits the development of efficient programs reaching all persons in the community. However, when resources become scarce, decisions are required as to how limited funds should be used. Commonly, countries opted for the short-term solution of sustaining curative service programs. In consequence, in the Third World as recently as 15 years ago, less than 5% of children were receiving vaccines against the common, wholly preventable and uniformly serious diseases such as measles, pertussis, poliomyelitis and tetanus. At that time, whole wards of hospitals were occupied by children with these wholly preventable illnesses. Eighty to 90 percent of government health budgets were assigned for curative services despite the extraordinarily favorable cost-benefit ratios for disease prevention by vaccines. Modest shifts in these allocations have now begun to occur but they are far from institutionalized. Parenthetically, lest you believe that the preoccupation with sickness care is exclusive to the Third World, I would point out that today less than half of those with so-called health insurance in the U.S. are entitled to vaccination.

Third World immunization programs changed dramatically with encouragement from the international community and donors. But, now just as the program has passed the mark of 80% vaccination coverage, donor fatigue has begun to set in. There is an increasing feeling that having "solved" this challenge, it is time to move on to something else, long before immunization has become an institutionalized or sustainable activity. This is but the first of the immediate challenges.

A second challenge pertains to research. As Gordon has pointed out, basic research now offers a host of new insights and new tools, so many as to make it difficult to decide which opportunities deserve highest priority. However, few of the possible initiatives are yet being pursued and the limiting factor is resources. The private sector has little incentive to invest and the public sector has not traditionally done so. This simple fact is vividly illustrated by the fact that none of the now commonly used vaccines is fully satisfactory either in potency or heat stability but none has been improved in more than 20 years. Private investment in vaccine research, to the extent it exists, is almost exclusively for vaccines which can be sold in the industrialized countries -- vaccines for AIDS, hemophilus influenzae and hepatitis A and B. There is little interest in vaccines against such as malaria or other parasitic diseases, leprosy or dengue.

Vaccine manufacturers rightly point out that there is little financial incentive to make the necessarily large investments to develop a vaccine and bring it to market. To recover the research and development costs, vaccines have to be appropriately priced and the price, reflecting a limited market, is initially high. Hepatitis B vaccine, for example, is selling for nearly \$100 for three doses. This reflects, in part, the unique nature of vaccines. The most successful require only one or a few doses and protect for a lifetime. The research costs are thus apportioned over a much smaller number of units than is the case for a drug which may be taken by countless patients perhaps 2 to 4 times a day for weeks or months. One may logically argue, and with data, that the investment in a "costly" vaccine saves on treatment costs in the long term. However, the payoff is not immediate but long-term. Moreover, purchasers of vaccine have become accustomed to the much lower costs of long-established vaccines whose R&D costs have been recouped years or decades before.

The public sector, including such as medical research councils and our own NIH, have likewise invested only modestly in vaccine research. In part, this reflects attitudes of the basic research community which regard vaccine research as "applied" or "developmental" and thus of less fundamental interest. Field testing and product improvement are often considered to be a private sector responsibility, much as is the case with pharmaceuticals. However, field testing of a vaccine is a substantially different proposition than the comparable clinical testing of a drug. Both the public and private sectors are reluctant to assume responsibility for this crucial phase and liability issues loom large to deter them.

A further problem is that, to date, international vaccine purchases have largely been by UNICEF and bilateral agencies, none of which have exhibited either capacity or interest in research.

Finally, let me turn to yet a third, vexing problem -- vaccine production. Most vaccine is produced in the industrialized countries and purchased for use in the Third World. Logic would suggest the desirability of local production at least in the more populous

countries of such as China, Brazil, Mexico, Nigeria and India. Regrettably, this is a challenge to which little attention has been given. Some countries have initiated limited scale local production or repackaging but with poor or no quality control -- yet another issue, largely ignored to date. In consequence, some seriously deficient vaccines are in use; vaccine failures are a problem as might be expected; and, as yet, the laborious but necessary task of building needed institutions and training of personnel has barely begun.

Even sustaining existing production capacity is a challenge. Vaccine manufacturers are often a small component of a larger pharmaceutical company or, indeed, a commercial conglomerate and are said to generate such limited revenues that they are of little interest to the parent company. In the United States, when liability issues became an acute problem, many such companies simply closed down their vaccine production facilities. Today, the commonly used vaccines in the U.S. are each produced by a single company. It is wholly unclear as to what the U.S. would do if one of these companies ceased production and yet this has been threatened.

Summary:

Developing and providing vaccines is a vastly different task and challenge than providing pharmaceuticals. It has taken far too long to begin to appreciate this. Because it has been so long neglected, effective institutions and mechanisms to deal with such as vaccine research and development, production and quality control have yet to emerge but they are vital. The effort requires and will require an imaginative amalgam of public/private sector efforts; basic and applied research; and cooperative programs embracing national and international agencies. Fortunately, there has been a small cadre, many at this School, who have successfully argued that immunization is not a fad, a passing fancy but, rather, it is the major supporting pillar for the future of prevention. And, indeed, if we ever expect to deal meaningfully with HIV infection, it appears to be the only approach.