RESPONSE -- JENNER MEDAL
Royal Society of Medicine
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I well appreciate the distinction and honour conferred by award of the Jenner Medal and am profoundly grateful to the Council of the Royal Society of Mcdicine and cspccially to you, the members of the Section of Epidemiology and Public Health. Understandably, the Jenner Medal bears for me a special meaning, having spent a substantial part of my professional life striving to make redundant Jenner's great gift to the world--smallpox vaccine--only to find that I, as an expert in smallpox, had myself become redundant. Meanwhile, that vaccine which we thought we had rendered redundant has undergone a marvelous resurrection as the base for a variety of recombinant vaccine products, including several candidatc HIV vaccinc strains.

It is difficult to conceive of Jenner's world of 200 years ago and to appreciate fully what vaccination would mean to the citizens of that time. Data from Glasgow, a city then known for the completeness of its statistics, document the fact that in the immediate prevaccination era (i.e., 1783-1800) 50% of children died before reaching 10 years of age and of that number, 40% died of smallpox. By 1810, only a decade later, smallpox deaths had dropped by four-fifths.

There is no question but that the availability of a smallpox vaccine marked an historic milestone in man's struggle against disease and so the names Edward Jenner; Sara Nelmes the milkmaid; James Phipps, the young vaccinee; and even Blossom the cow echo through history.

It is significant to note that Jenner did not seek to enrich himself by commercializing his discovery although he could have. Variolation, i.e., the inoculation of infectious smallpox material, had been widely practiced in England in the late 1700s. Sutton and his sons, some of the best-known of the variolators, kept their methods secret and charged from three to seven pounds each for those he inoculated, with fees as high as 20 pounds for the more prosperous (200 times those amounts in today's currency). It was suggested to Jenner that he do likewise. He declined. And so, from the first, vaccination was generally treated as a social good and provided at public expense or for modest fees, an important policy which has continued as other vaccines have been introduced for use.

Jenner foresaw a bright future when in 1801 he wrote of vaccination: "the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practise." Ultimately, of course, this occurred but not until 180 years later. Why the delay?

The vaccine itself proved to be the vexing barrier. Until the late 1800s, the propagation of vaccine was by arm to arm transfer, from one vaccinee to the next. Vaccine strains failed sometimes to be transmitted successfully and new strains of cowpox had to be found, often with great difficulty. Although protection was conferred on many people, there was risk of acquiring syphilis or hepatitis or tetanus. Successful vaccination in the tropics proved especially problematic.

Three important discoveries, two by Londoners, opened the way for large-scale production of smallpox vaccine and a thermostable product paved the way for the eradication of smallpox. The first discovery was by Italian investigators who found that

vaccine could be grown on the scarified skin of calves. This permitted large volumes of virus to be produced and harvested. But bacterial contamination of this product seriously compromised vaccine potency until Dr. Sydney Copeman, a Londoner, showed that glycerol, when added to the vaccine, largely stopped bacterial growth. This permitted the harvested vaccine to be packaged and distributed in capillary tubes. Still, the virus in this form remained very thermolabile and a problem for use in warm climates. However, another Londoner, Leslie Collier at the Lister Institute, solved that problem in the early 1950s by perfecting a method for freeze-drying smallpox vaccine, much as one would freeze-dry coffee. His vaccine product remained stable for six months or more at temperatures of 45 degrees Centigrade.

Thus, by the late 1950s, a potent, stable vaccine, suitable for use in the tropics was at last available. The tools were in hand but no laboratories then had the capacity to produce the hundreds of millions of doses needed. As we in WHO saw it at that time, production in the developing world itself was the only reasonable course of action. But this required technology transfer and training, always sensitive issues for manufacturers. However, none of the major production laboratories hesitated when asked to assist. Professor Colin Kaplan of the Lister Institute as well as scientific colleagues from laboratories in Canada, Russia, Holland and the USA participated in the development of laboratories on three continents. So successful was this effort that within five years, 80% of all smallpox vaccine was being produced in the developing world and independent assays revealed essentially all vaccine to be fully potent and stable. Thus, the sine qua non for eradication--ample supplies of a potent and stable vaccine--were assured.

The point to be emphasized is that after discovery of a vaccine, there are a substantial number of critical steps in development before desired goals can be achieved, i.e., the large-scale production of an affordable vaccine product suitable for widespread use in the field. However important such aspects of applied research and development, they are seldom lauded, appreciated or even well understood by the scientific community. In today's world, it is precisely this facet of vaccine development which now constitutes our critical barrier to progress. To illustrate, of the six antigens now in use in the WHO global immunization program, none are entirely satisfactory with respect to potency and/or heat stability; neither have any undergone any improvement over the past 30 years.

There is a remarkable difference in the situation from that of little more than a decade ago when both vaccine research and vaccine delivery in the field were languishing. Stunning changes have occurred. To wit, in the developing world vaccine coverage for the six major antigens of WHO's global program on immunization has risen from less than 5% in 1975 to 20% in 1985 and to 80% today. There is now in place a delivery system of unprecedented scope reaching across the world and into most of its inhospitable regions, delivering these antigens for diphtheria, pertussis, tetanus measles, polio and tuberculosis; and, in the course of so doing, preventing three million deaths per year. In the USA, pre-school vaccine coverage has increased from perhaps 60 to 90%; and you in the United Kingdom have led the world in attaining 95% levels for all the recommended vaccines. Meanwhile the World Bank's 1993 World Development Report has identified immunization as, by far, the most cost-beneficial of all medical procedures

and now, even the poorest developing countries are beginning to fund vaccine purchase from national budgets. A remarkable foundation has been laid.

At the same time, research on new vaccines has grown exponentially, funded in part by government, and in part by industry; and fueled by a rapidly increasing understanding of the human immune system, microbial genetics and mechanisms of pathogenesis. A decade ago, a conference on vaccination would draw hundreds of participants; a conference today on respiratory vaccines alone will attract thousands. The quandary is no longer one of endeavoring to identify productive lines of research but rather, trying to decide which of a host of productive lines to pursue. The most recent National Institutes of Health inventory of vaccine development, documents some 150 known vaccine products at various stages of research, of which 35 are in phase III human trials. Effective vaccines against malaria, tuberculosis and AIDS would in each instance represent an additional giant step forward. All pose special problems but there are observations with respect to each of these diseases which argue persuasively the case that an effective or, in the case of tuberculosis, a more effective vaccine should be possible.

And, as you know, the potential for immunization has now begun to be realized well beyond the infectious disease field. The first vaccine designed to prevent cancer--hepatitis B--is now in widespread use and will have a major impact on one of Asia's most important cancers, that of the liver. Experimental studies indicate that an anti-papilloma virus vaccine should be feasible. If so, cancer of the cervix in the next generation could become a rare disease. And, with increasing recognition of the number and diversity of auto-immune disorders, studies are in progress utilizing T cell vaccines in an effort to

remove offending T cell subsets. Such vaccines could have broad implications for diseases such as rheumatoid arthritis, multiple sclerosis and perhaps even atherosclerosis.

Our principal concerns as we look toward 21st-century vaccine policies are neither a dearth of potential products or a lack of systems to deliver them but, rather, an apparent surfeit of riches. The word "apparent", however, is the operative word.

There is yet another critical element in the equation which has not yet been addressed, let alone seriously taken up. With many different products, produced by a variety of different manufacturers, there will be and, in fact, are today unresolved conflicts as to how best to accommodate these sensibly in immunization schedules which would not necessitate three, four or five inoculations at a single visit or, alternatively, require eight, ten or twelve monthly visits. Multivalent products, as now exemplified by MMR or DTP, are one answer although it is apparent that there are difficult problems with potency, in particular, with each added antigen. The use of sustained release preparations could serve to decrease the need for multiple injections as could the administration of vaccines orally or by aerosol. Yet another approach is to combine several antigens in a single carrier agent such as vaccinia or salmonella. Work is in progress in all of these areas.

But, finally, somehow or other, methods must be found to produce the vaccine products inexpensively on a large scale and in a form suitable for field use. Let us not forget that the principal reason that Jenner's dream of smallpox eradication was <u>not</u> realized for 180 years relates in significant measure to the fact that adequate supplies of a potent, heat stable, inexpensive vaccine did not become available until the early 1960s.

What will be required are new initiatives involving unique types of cooperation which join private and public sector vaccine producers, vaccination program directors and the research community. So far, few efforts of this type have been made. However, I am confident that given the appropriate leadership and auspices, this effort could resolve what are now, in fact, the principal obstacles to progress in realizing the full benefits of immunization.