D.A. Henderson's remarks to the Programs Committee

April 1989 Meeting, Phoenix, Arizona

D.A. Henderson: I began my work in polio in '55 in introducing first the inactivated vaccine in the US and the oral vaccine, so I spent maybe ten years on this, left it and came back in again as chairman of a technical advisory group advising on polio eradication in the Americas. In the last few months, it has been proposed, I have been asked to serve as chairman of a similar group for the global program. Thus, I have become more involved with the questions of 'where the program is', 'what its problems are' and 'what do we do about it?'.

There are some problems. During the past twelve months, we have had a number of meetings in a number of different settings to examine the progress in the program in immunization, polio eradication in particular. Just to remind you briefly of the history of this program in immunization, it began in 1977, over twelve years ago. In the early eighties, UNICEF became very much involved with this, with its child survival programs, and Rotary embarked on its historic initiative of PolioPlus.

Then in 1985, the progress in polio control in the Americas proceeded so dramatically that a committee was convened, I was part of that committee, and we agreed that we could see the feasibility of eradication in the Americas. Until then, I think that a number of people had doubted that this was a possibility. We doubted that possibility for two reasons.

rapidly achieving standards, which are going to permit this to be accomplished but just barely, there is not a lot of room for latitude. As we look at the situation in Africa at this point, with the current vaccine, with the problems of Africa infrastructurally, it means that eradication in Africa is simply not possible. In Asia, it is a mixed situation. In part cold chain and some of the logistics are there, but we also know that when you have dense crowding of populations, a lot of movement of people, which we do have in Asia to a degree that you don't have in Africa or Latin America, that you have problems, in that the virus is able to move around much more rapidly.

Last year, the World Health Assembly in May, declared that the global eradication of polio by the year 2000 should be an objective, and all the countries unanimously approved this goal. At the same time, in the discussions leading up to this, and at the time of the meeting, it was recognized that this is not a feasible accomplishment unless there were better vaccines available. The goal should be there, provided that better vaccines are available. The characteristics of the vaccine would require that fewer doses would need to be given, greater stability should be a possibility. Over the past eight months there have been a series of meetings with people who are knowledgeable in the field of vaccine development and strategically we would see the need to develop a vaccine not later than 1995. The tests to develop a vaccine is not an overnight proposition, it takes you a number of years. Right at this point, with a very decided major effort now, the better vaccines by 1995 is probably the most realistic, early, in fact a little optimistic, figure that we can come up with. The three directions that they have

whatever it is down to one, and provide protection. It looks very encouraging, and the first discussions have just been held with a company in Cincinnati which has been doing this with pharmaceutical preparations.

Now each of these are major efforts for the time not only to develop the vaccine, but you have to test it in the field, and it is going to take a commitment of some not inconsiderable amount of money. We have no idea what that amount of money would be, and I think it is hard to guess because the hope would be that we would be able to get some of the manufacturers to do some of the work, to get governments to contribute something to it. In a moment I will point out some of the problems. It is believed that a commitment on the order of ten million dollars a year for five years is going to be required to do this job. That may be on the high side, but it is an order of magnitude.

The problem that is being encountered at the present time, is as follows: Manufacturers basically make their money by selling the oral polio vaccine to industrialized countries. That is where their profit is. The vaccine sold for use in the developing countries represents increment production costs. So that they are financing basically the plant and their ongoing costs out of what is sold in the industrialized countries.

The increment cost is what we pay for the vaccine, up to three or four cents but it is a lot more expensive in this country. None of the manufacturers see any of these new vaccines as having applicability in

UNDP and the World Bank have supported some research for some activities but neither of them have provided very much money to any research project. They tend to be much more related to individual country activities and major programs. This is a bit out of their sphere. I have had discussions with Mr. Tim Rothermill from UNDP and he is cautiously, "in view of where you are and what the problem is, maybe we can come up with some money on this and I will look into it". WHO ~~and the~~ administers a program of research, while its total research budget can't be more than a few hundred thousand dollars, basically administers monies made available from other sources and finally we look to such as Rockefeller which does put in some money now, but again their resources are not terribly extensive.

For Rotary, this has not been in your portfolio either. The question at this point, in talking with the variety of people and I have raised this question in light of saying that if we are going to look at a global program, we had better look very carefully at the strategy, and the tools that we have. The question posed, "what are we going to do?", and fundamentally the answer is that we really need something like a Manhattan project for polio vaccine. I've imagined a carefully supervised program of targeted research to get the vaccine that we need to eradicate polio. If we don't do that we are not going to eradicate polio we are going to go on into the year 2000, still trying to control polio in countries in Africa south of the Sahara, much of the Indian subcontinent, Laos, Cambodia, Viet Nam, Indonesia those areas are going to continue to have polio I think as far as we can make out based on experience to date.

require an enormous effort and that Rotary and everybody else who was interested in it was going to have to be prepared to do some new thinking and to be more flexible in the way that we spend our money.

Our problem is in part that we receive money from Rotarians who don't horse around the world and why I think it is clear that their expectation is that we are going to eradicate polio, we sold the program to them with the idea that this money would be used exclusively to buy vaccines, it would not be used for salaries, or transportation, or research, or a lot of other things, and now it is becoming increasingly obvious that we are going to have to, if we want to achieve our ultimate goal that we are going to be more flexible and we may have to find a way to explain that to the Rotary world, if we can get their consent in some way. Are there any questions around the table? Trustees? Consultants? Trustees-Elect?

Jacob John: Let me highlight one point. Although Rotarians are simple minded, let me take you back to the first two meetings of the we are able to take that focus on the quick job of polio fixing to do more for the Indian state who joined the worldwide effort on child survival. And 42,500 people the concept was accepted at the first two meetings at considerable personal cost to two of us, myself and Ken Hobbs at the I think that there was a lot of (sneeze) at the time. I fully endorse Dr. Henderson's approach to this issue and I think that at the whole time I have been totally dedicated from that point of view. I just want to say that.

Keller: I appreciate your comment. Hector?

Hector Acuna: Well, I have no question about this statement which was known

capability, or the technical within our group. We have people, but as an organization, that's not our ball of wax. It seems to me that of all the funding sources available, it is going to take a cooperative effort by everyone to achieve the ultimate goal. Some people work better in some areas, and other people can finance and work better in other areas. My inclination is to say that we are interested in the final goal and we will contribute to the best of our ability in whatever way will contribute to the total effort of Rotarians who don't even know that WHO is working on immunization. When we got started we thought that this was going to be our baby. It came as an enormous shock to Rotarians all over the world that UNICEF and WHO had been working for forty years on this job. I think that we would never say no, but, use us sparingly as a research resource.

D.A. Henderson: Let me comment on this. I think Dr. Acuna's point is quite correct. Indeed, smallpox was stopped in a whole lot of countries using this very unstable liquid vaccine. As we review the progress around the world and where we are on polio it looks like the countries in which we can stop transmission of polio are precisely those where is was possible to stop it with the liquid smallpox vaccine. The areas where we have the real problems which are Africa, the Indian subcontinent, Indonesia that without the freeze-dried vaccine we would never have succeeded. There is a comparability here in that you can go pretty far such as in Latin America, you can go pretty far in China because of their structure and organization and then we get into other countries with a different political social managerial setup a different set of criteria you've got problems. At this stage, what we are looking at is the question of can there be set up something like as they call it "Manhattan Project"? as

India I think is one exception to that, we are not seeing the effects in India at all at this point. But in most countries we are seeing diminished paralytic disease. We are also seeing a change in the way that people are thinking about how vaccines have to be given (end of side A)

.....participation activities which I think is the key to the future for all vaccines for the delivery of all vaccines. It is taking them a while to learn how to do this and to do this well. I would say to keep this moving and to keep again gradually improving skills and abilities to do these things and controlling polio, it is not going for naught, I think is very important to anticipate now that at some point we are going to see no polio in certain parts of the world without better tools. I think based on what we have seen in the Americas now, based on what we are seeing in other countries, it is quite clear that this is just a tough problem. With the tools we have, this is just not on to really totally stop polio. Simply because of in Africa for example, the resources, the transport all those other issues the temperature, the failure of the vaccines to be as effective as they are in the temperate climates, all of these things combine to make it just a very difficult proposition. This is a cold, hard calculating look: Can we do it? Based on the experience we have, where are we now, and what are we going to do about it?

Keller: It is interesting that in the world of science and medicine we are so used to advances we are almost the victims of our own success. I do medical malpractice defense work and I feel so sorry for the obstetricians. They produce the expectation of perfect babies. When it doesn't happen, then parents now look around for someone to sue and its a tragedy because there is no such thing as 100% perfection.

meeting, that having created a climate in which people were demanding, governments are demanding this sort of thing that we have a responsibility to help achieve it.

D.A. Henderson: In my opinion this has been a very positive thing for the countries of the world. Polio in all countries has not been the most important problem that they face. No question. But it is an important problem and to do something about. There are other problems that you have but you can't do much about it, malaria for example. But here you can do something about it and if the whole phenomenon of paralyzed children that go on through life this way, its a formidable problem and burden in the community. It is amazing the response we have in countries. Most countries throughout the world are really interested in this program, more so than they are with programs that might address more major problems, the political will is certainly there in a way that is not in other ways. I think this can be a tremendous contribution in development health services beyond just eradication of polio.

Archer: You have brightened my day. I have been wandering around the world saying with reference to our PolioPlus campaigns, that the easy part is past, the hard part is still ahead. I have been saying that to a lot of Rotarians. Raising the money was the easy part. The hard part is to continue to deliver the vaccine as we know today, and feel that in light of the additional information that you demonstrated to this group this morning opens up some new areas of concern that we have and when you mention that Rotary should really satisfactorily answer the problem, they have to have a research program part of a research program, the size of the Manhattan project, so having been involved in that I know what you are saying, in that and I am sure that others here have that

I may, to ask a question I am not a technical person, is there any recruitment in your thinking that is needed in the mode of delivery of the current vaccines? That would make it more effective to those areas in which we consider less satisfactorily covered?

D.A. Henderson: Yes, there are some things that can be done. In the last two years a number of studies have begun to look at the mix of these three types of vaccines as you put them in, or change that you get a better response, a lot can be done on the operational side to mobilize people and to figure out how to best deliver it under a variety of different circumstances, different governments, different health systems and that I think can restrain a program, and there are additional people we could put in there. There are a lot of other things that being done in terms of ways to detect cases, ways to isolate the virus so that we've got surveillance we know where it is, we are learning something about the epidemiology of it which at this point suggests to us that it is very much like smallpox it keeps going, primarily, in your major urban conglomerates and your more densely populated areas and is not continually circulating out to more remote areas. This gives us great encouragement because indeed this calls then for the concentration of efforts strategic ~~including~~ planning efforts in areas that are the more densely populated and that they are also the more accessible. And so we found this with smallpox that we didn't do very much at the Amazon basin, we didn't do much in the Himalayas, although villages that are so remote, until the end, and that was only to confirm that smallpox wasn't there. It just had died out. If we really focus in particularly strategic areas and the more accessible areas, we can have a major effect. There are a variety of things that as we move into this eradication of polio in the Americas you've got a lot of advances that we are looking at.

that commitment in many ways. But that was in a monetary technical sense, the basis for which we ended up deciding that we needed to raise US$120. You had to multiply five years times the number of children in the world, the amount of vaccine you needed, how much it costs and you've got $120 million dollars. Herb was very much involved in constructing that particular decision and multiplication. But, as we see from some of the graphs we have to deal with next, some countries have already expended that allotment which would have been their "fair share" based on that five-year type of commitment and are asking for add-ons of one year, two years, whatever it is. The original idea was that the government would commit as they did, that they would continue the program after five years, that it would not be a forever continuation, by Rotary support because that would be potentially infinite, if eradication did not occur. So with that being a basic commitment we now of course are faced in certain countries with the problem of, well, if we don't provide continuing support, will they just drop immunization completely, or effectively drop it in that country, and set us back many years. Secondly, the issue which Dr. Henderson has brought forward, that even if we do provide this vaccine, given the circumstances that it has to be given under, and the way it is going, we will certainly in at least certain areas of the world, not eradicate polio given this particular program. And so I think that we will have to look at, perhaps we can ask Dr. Henderson to give us a report back after the subsequent meetings which will be held this fall, is kind of a further global view of where we are in, one controlling, and two eradicating polio, and we have to monitor this very carefully over the next few years to be sure that we are focussing our monies

poorest nations of the world the per capita spending on public health is going down, not up. And by a magnitude of 50%. In Nigeria, the proposal there before you-their declining GNP last year alone was 8%. Now what is on the prospect to turn this whole thing around, perhaps a diminution in armament expenditures is the only bright spot that might begin to pour more resources into human development. In terms of armament expenditures it is such a small amount that would be needed to turn the tide in this . Now one final comment, in our second round grants we are trying to effect a much closer coordination cooperation among all the donor agencies so as to maximize the efficiency of the grant. It takes two forms. If you approve of a phase-two grant, or a second round grant, it demands that there be multi-agency planning, and it also incorporates, except for the countries of the most severe economic need, a phasing down in our input. That basic plan is not hard-hearted, it is just a recognition of the realism that by the time our grant for polio vaccine runs out, the country will not be faced with a budgetary hole, but will have been building up its own national budget to meet that. Thank you.

Acuna: I think the participation, the leadership of world health assembly will be very important to apply the necessary pressure in governments to help ministers around the world. Some places we can help on a purely personal basis, but the muscle ... And we have participated in this extraordinary work that you are doing. I appreciate and I thank Rotary and you all for the opportunity to be of service to the committee and the serving Rotary up until now, but mostly I wanted to tell you that I have really enjoyed Rotary and look forward to being a District Governor. Thank you.

secretariat was held in December,1988, to review the different approaches being made. The full report of that meeting is not yet available, but the following is a summary based on discussions with some of the attendees.

Each of the three major approaches extensively discussed has advantages and potential disadvantages. The first two priorities are seen to be:

1. 'Reassortant' polio virus strains; replacement of part of the genome coding for structural proteins of type 1 virus with the appropriate part of the genome of types 3 or 2. This approach has mainly been pioneered by Japanese scientists. It would help on two fronts - the genetic instability of type 3 would no longer be of concern, and the problem of viral interference would diminish. This approach is well advanced and seems to hold great promise.
2. Further attenuation of type 3 virus. This involves the introduction of additional mutations into the 5^1 end of the type 3 genome where the crucial attenuating site (bp 472) occurs.

The third approach is the production of antigenically hybrid (chimeric) viruses. This is the insertion of 'neutralizing' amino acid sequences from type 2 or 3 into the VP1 of type 1 virus. Though considerable progress has been made with this approach, some potential disadvantages need to be investigated.

In addition to the above, there is also reason to believe that a molecular approach to improve the thermostability of the vaccine is feasible. This together with studies on improved stabilizers and conditions of lyophilization could result in additional improvements to future vaccines.

To make the necessary impact in the short time available, this research needs an immediate and very substantial influx of funds.

this area of controlled release formulations, based in the first place on the use of tetanus toxoid as an appropriate test antigen as the funds available (c.$150,000) would only support this limited approach. This antigen was chosen because it is part of the EPI schedule, is readily available and a single shot injection would have a major impact upon maternal and neonatal mortality due to tetanus infection.

Appropriate bodies (Pharmaceutical firms, Universities, etc) were therefore approached and 23 replies received, indicating interest in participating in such research. A short listing was made and after interview, 4 groups chosen to construct formulations so as to deliver a dose of antigen under certain defined conditions, such as constant or pulsed release over different periods of time. This approach will involve detailed planning of the mechanics of assessing the efficacy of the immunization schedule.

With greatly increased funding, this work could proceed on a much broader front. Specifically, we propose that studies be initiated on the construction and testing of formulations containing (separately) DPT and IPV: modifications to the delivery of these two vaccines would have an early impact on the EPI and on the Polio Eradication Programme. The savings in total cost and labor in vaccine delivery are expected to be in the long term at least an order of magnitude greater than the cost of the Research and Development component of this approach.