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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.

One, the oral vaccine is very unstable. It does not do well under certain temperatures, and therefore you have to maintain a very elaborate system of refrigeration to get the vaccine to the recipient while it is cold.

Second, we know that in the tropical areas the vaccine performs much less satisfactorily than it does in the temperate climes. The variety of possible reasons for this, some of these relate to other viruses which interfere with the take or growth of the virus in the intestinal tract, some of it may have to do with nutrition, there may be other causes, but the fact is that is sometimes we will do very well on a tropical area and then at other times we will not do well. It is a very undependable vaccine, particularly in the tropical areas.

However, by 1985 the dramatic drop in polio incidence in Latin America suggested to us that it might be possible to eradicate polio in two to three years. We think, from our last meeting which was only a few months ago, we believe this is possible within two to three years. It is going to depend a lot on political stability in the Andean countries, as to whether this will be successful, but at the moment it looks very encouraging.

In reviewing what has been happening in the Americas has been perfectly apparent to us that it does require a very tightly managed system, we have to have a very well managed system for this to work. A reasonably good transport with a very carefully supervised cold chain and you need some pretty good personnel. As we see it, in the Americas, they are

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

identified that are at this point with the technology we have, with the research capabilities we have, and the state of the art, there are three directions that we can see.

1) To try to freeze-dry the vaccine. This was done with smallpox vaccine, like freeze drying coffee. If indeed it could be freeze dried, it might hope to achieve the stability of smallpox vaccine, which we did keep at room temperature for months, even in tropical areas. The prospects for success of this idea, those who are in the field guess that it may not be more than 40 to 50% possible. Work is beginning, and there are capable who can do this.

2) Genetically engineered vaccine. Instead of having three strains which you feed, the idea would be that you bring this down to one basically (put the three viruses together) and to feed that virus with the expectation that we might be able to reduce the number of doses to two and even conceivably one dose and get a very good response protection.

3) Look at the inactivated polio vaccine. Prospects are 85-90% for achievability. Very interestingly, we now give drugs by inoculation, and with various of the new plastic polymers you can get them to break down at various speeds and you can release a drug over a very long period of time. Curiously no one has done anything with this for vaccines. It is the belief that we could incorporate vaccines into some of these polymers and get a sustained release so that in effect what you might do indeed to reduce the number of doses of killed vaccine, 4, 3 or

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

the industrialized countries and so they are not very enthusiastic about doing any research, and making any investment. So we are getting very little in the way of activity on the part of the manufacturer. The National Institutes of Health does fund research, but they are committed to gear their programs to activities which will be of benefit to the citizens of the United States, in one way or another. This one is a little bit difficult for them to deal with because we have a satisfactory vaccine in the US, why develop another vaccine? More than that NIH has been stretched very thin because of having to commit so much to AIDS research, that the amount left for many other projects has been squeezed.

The Agency for International Development as we reviewed their program or portfolio, that basically they do not do much in the way of research. They provide comparatively little money for research outside of the development of the malaria vaccine, and the very little that they put in anything else. Whether we can change that or not, we are not certain. We are not optimistic that we are going to get a lot from them but, that would be another source.

International agencies present another problem. UNICEF has never funded research. This not in UNICEF's charter and they have never provided research. Will they provide money for research on this occasion? I don't know. I have talked with some of the people at UNICEF, Mr. Grant, Dr. Ramilgatswami (??), and conceivably we may be able to persuade UNICEF to put in a sum of money (2-3 million a year) perhaps, we don't know. That will be dependent on a major part on their board.

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.

At this stage, we are asking the question of a number of agencies and will be looking at this further with another meeting next month which we have asked a number of experts to come together to draw up a very specific program and the cost of a very specific program on the genetically engineered vaccine. We will ask another group to look at the sustained ~~of these~~ release preparations to come up with more specific costs, and we will be meeting again in September for the first formal meeting of our Global Technical Advisory group and this will be a major issue at that time. How do we proceed to get the tools that are needed? I think that realistically, where we are in terms of moving from control programs to eradication programs, which are of a very different order of magnitude. Controlling a disease is one thing, eradicating it is something of a higher order to do that we need very good tools. I think ~~that as~~ Mr. chairman, all I would have to offer as introduction, I would be happy to answer ~~these~~ questions.

Keller: You've given us a mouthful to chew on. I think Rotarians are a very simplistic bunch. We saw polio in the world, we knew it could be gotten rid of. We got rid of it in the US, in Western Europe, we can get rid of it. We'll just raise US$120 million and we'll buy a lot of vaccine and dump it on the world and that will be the end of polio.

And it is coming to us very late that the logistics involved are enormously complex and the fact the WHA took what I thought was a very courageous step to aim at eradication instead of 'control', I think it was representative to me that this meant a change of fifty years in the time schedule. It was moved ahead fifty years. That was going to

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

for some time, or suspected for some time anyway. The one thing I would like to mention is the fact that even dealing with smallpox we began the efforts to eradicate this smallpox with a non-dried the development of the freeze-dried vaccine was of course the early point to make the effort to eradicate smallpox possible. I suspect that likewise in the case of polio there are possibilities of the freeze-dried vaccine if this is decided will be developed within a reasonable time to be used, precisely in those areas of the world where the recipient is a lot more cumbersome than the operation of polio 3. At this stage I feel that we should not deviate from our purpose and continue our activities to eradicate polio because we are still on the right track. There are indications that we are going to eradicate polio from the Americas in a reasonable time, possibly from certain areas in Africa itself. But I do agree with Dr. Henderson that we are going to find extreme difficulties in the next few years in Africa that would deal with the eradication. My feeling is that we should be a little more, not conformist, but rather optimistic about the fact that we'll find better vaccines within the next few years to give in precisely those types of situations. But in the meantime, I think that we should begin toward our main objective and deal with the polio in the parts of the world which are susceptible to the use and effectively as we are doing in the Americas and the other parts of the world.

Keller: But the point that you are making moved me to make an observation. Partly because of the nature of our organization, we were volunteers from every corner of the world subject to enormous differences in pressures and so on back home. I think that we have never been well set up to get involved in research type work. We don't have the oversight

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

some have referred to it. That would be a collaborative effort of a number of different agencies contributing to a central managed research operation with good people managing us. I think the feeling is that that would be the structure we would look for not to say WHO doing a piece and UNICEF doing a piece and somebody else doing a piece which is very difficult to coordinate but we got to put this together as a coherent managed project. To see if indeed the funds can be identified for this to permit this to move ahead very rapidly because I think right now with what is being done and lots of people working in the field they are working on very small budgets and are putting very little effort into it and we are just not going to get a vaccine at the rate we are going.

Pieter Sablon: While you are on this I have a question. We have limited on the available we have committed ourselves to a program to which the world You have shown to us new aspects of the whole thing about what to do. My question would be, 'is it wise to continue the way that we are doing now', or with what you have found out or WHO slowing down of some way of going away. You have indicated that what we do is not going to serve the purpose finally so if we continue just because we have committed ourselves to do something, our means will not. Can you from the practical side already say now, that this will be one of our main problems to, if what we are doing now is wrong, what would be the next step anyhow, if it is right, then it is right go on, but be sure you need more money in the future? What is the situation in your eyes?

D.A. Henderson: My feeling on this would be that what you are doing now is the right thing. It is not that the vaccine going out there is having no effect, In in most countries, you are seeing diminished levels of polio.

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.

Sablon: Let me just add something. We should be finishing our own objectives here which was to achieve probable possible eradication of polio by the year 2005. And what are political decisions are the implication that they would like to give all the other American health organizations, the position of the governments of this continent to see that we say in 1990 which we won't see of course, it will take a few more years obviously. Now, the Assembly has decided to reach that particular goal by the year 2000. Now it is a political decision obviously which will provide additional resources and impetus to the polio drive throughout the world. But, let's not confuse the issue, the political issues, the real issues that Rotary International has undertaken.

Keller : Rotary International started into this with the idea of eradication, didn't we? That was our original goal. I think technically we used the word control. I think Rotarians spelled control - eradication. I say among non-technical people it was a concept. Well, we have had an interesting discussion here and I think the advice we are receiving is that we should continue with our present structure, doing the things that we are doing, but realize that stronger efforts are going to be needed over the next twelve years in order to accomplish the ultimate goal. We have been warned now, thank you very much, I don't know what we are going to do with the warning, but at least we are not in the dark. I think we are on board, we have signed up for the duration.

D.A. Henderson: I think that the Rotary initiative has been the major factor that has tipped the scales to produce this interest in eradication and without that initiative, I do not think the goal would have been set.

Keller: That puts a responsibility on us, and we talked about this at our last

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

concept. However, I entertain the feeling that what we are doing is a tremendously valuable contribution to the battle which can be characterized as a battle, whenever you enter a battle you may not head into the battle in the beginning with the best weapons, but what weapons you will need before the battle is over. For example, our current program, I consider it very very important because it will demonstrate absolutely whether or not the current attack will be globally successful. You've indicated that it will not be globally successful, but that information in itself is important to us. In connection with the potential or the current mode being successful in the Americas. The Americas extend from the North Pole to the South Pole which includes all weather conditions that are common around the world. If you take any orange segment of the world, you just duplicate it all around. If you can be successful in the Americas, but not in other segments, then it tells us that there is something more than the weather the conditions concerning these areas, that will teach us something else. In addition, we know that there will be some success, we do not know how far it will go. But that some success will reduce the need for the extent of the forces indicated. In those areas that become absolutely by the continuous today. It will also serve to demonstrate to some sophisticated societies, that there society is not as sophisticated as they think it is, and require them to be examined by another society, in order to handle a problem as basic as the elimination of polio. An event that can take place in other societies . Although I see that we are entering into a larger understanding of the problem since the continuance of our present attack is essential as providing a base on which a more sophisticated attack can be launched. I would like, if

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.

Huntley: I had no conception, Hugh, as to the amount of work that is going on around the world on a daily basis, the meetings, the projects, the activities, the enormous amount of activity going on all over the world.

D.A. Henderson: You might just want to take a look at this for your own information because I found it very striking.

Ken Hobbs: If I hear you correctly, and you appeal to my advice in Africa, for example, it presents a very different (Sub-Saharan Africa) are you advising us or recommending to us applications for advance, it should rather be withheld in those areas till a later date? Is that what you are saying?

D.A. Henderson: No, I am not. What I would suggest is that to look at it realistically, I think there are, the program should continue in Africa, that there is effective control of polio that is possible, that there is a need to begin to get better at the social mobilization delivery operations they have, but to recognize that it is going to take a longer time frame to get rid of polio so that between 1995 and the year 2000 still going to be polio throughout Africa, I think. It is a problem then of hopefully having a new vaccine, and new vaccines which are going carry it over the hump to do whatever else needs to be done. So that you look at a longer time frame in the African countries.

Keller: Two things, I am going to ask John to make his comment, then I am going to ask Herb to make any observations that he wants to and then we are going to break for coffee. John?

John Sever: Just to remind you that when we started the effort, the original planning of Polio 2005, the commitment which was made and accepted by Rotary was to provide vaccine for five years to any country that had a WHO-approved vaccine program. Now, obviously many people interpreted

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

appropriately, that in those countries that we see here are asking for add-ons past the five year support, that those monies are really being well directed towards areas that need that kind of supplementation. We therefore take the global look at the need to get good results for the monies that have been contributed, even though the initial agreement was to provide vaccine for five years.

D.A.: You have put your finger on something that concerns me, and that is going back to the well so often then in different countries that I think that our resources are finite not infinite, and I think we have to be careful in those several projects here where the original grant was $50,000 and now they are back for $500,000 and, Herb?

Herb Pigman: Well I was very pleased to hear Dr. Henderson credit Rotary with perhaps tipping the scale towards the decision of WHA to go for eradication, and the resolution which will be before the WHA for formal adoption of this goal, or the plan I should say, two weeks from now, specifically praises Rotary International for its course of action. Dr. Henderson also said that our present course is a correct one, which I was very happy to hear. Even though we face rough terrain ahead, I think that I have also heard from many sources and meetings that we have got to do the job with the tools presently available, vaccines presently available. That is now obviously beginning to change. Whether or not we can do the job with the tools presently available, that is OPV in its present form, and the new enhanced IPV which shows very good promise, depends a great deal on factors which are beyond the control of the health community and by that I allude to the total world economic condition. We have a very creaky vehicle for the delivery of vaccines, and the vehicle is getting worse in many countries. In the 30 or 40

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.

THE WHO/EPI POLIO ERADICATION CAMPAIGN: THE NEED FOR IMPROVED ORAL VACCINES.

The forty-first World Health Assembly in 1988 resolved to initiate a campaign to eradicate poliomyelitis from the world by the year 2000. Most polio immunizations in the world (and all carried out by EPI) use the oral polio vaccine, OPV - the Sabin attenuated types 1, 2 and 3 viruses. In some developed countries, vaccination is carried out using inactivated polio vaccine, IPV. Several countries are considering or recommending a change to a mixed vaccination schedule - IPV with or followed by OPV. This approach might be difficult to implement in some developing countries, due to the cost of the IPV and logistic difficulties.

Many believe that if world eradication (versus control) is to be achieved, an improved oral vaccine will need to be developed. If this goal is accepted, the time schedule is very tight as such a vaccine would need to be available for use in the field by 1995.

The current OPV has the following characteristics:

1. Type 2 is both immunologically dominant and has the best growth characteristics;
2. Genetically, type 1 is the most stable. Type 3 is the most unstable with a rate of reversion to virulence and a frequency of paralysis cases which is too high if eradication is the goal;
3. Interference with viral replication is thought to occur, particularly with type 3;
4. There is sometimes poor seroconversion after vaccination in developing countries (probably related to 3.).

The Steering Committee (S.C.) for poliomyelitis/hepatitis A of the WHO Programme for Vaccine Development (PVD) has helped to coordinate, and in some areas, extensively supported research directed towards these and some related problems. A meeting of interested researchers, SC members and WHO PVD and EPI

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.

SIMPLIFIED VACCINE DELIVERY SCHEDULES.

The present schedule for the Expanded Programme of Immunization (EPI) vaccine delivery involves five visits; at birth, 6, 10 and 14 weeks and at 9 months. This is a strict requirement to the extent that inclusion of further vaccines into the schedule would need to conform to this timetable and not introduce additional visits of health personnel. It involves parenteral administration of DPT and oral administration of polio at 6, 10 and 14 weeks. The former requires relatively skilled health personnel.

Three modifications would greatly simplify the task of vaccinating the world's children. They are fewer visits required for injections, oral administration of vaccines and multivalent vaccines. This proposal concentrates on the first stage.

Stage 1. Administration of non-infectious vaccines as a single - perhaps two - injections, instead of the three or more injections required at present; this would decrease the need for skilled personnel at two of the above five visits. This could be achieved through the use of controlled release formulations, as is already practised for some purposes in the veterinary and pharmaceutical industries. There is every reason to believe that this approach would be successful; experience in the WHO Human Reproduction Programme (HRP) with a diphtheria toxoid (DT): hCG peptide formulation has shown prolonged production of anti-DT antibody in rabbits for many months after a single injection (Stolle Research and Development Co. with HRP).

The WHO Programme for Vaccine Development (P.V.D.) in association with EPI recently initiated a Trans-Disease Vaccinology Component to develop technologies for vaccine delivery which would be applicable to vaccines in general. It received funding from UNDP and The Rockefeller Foundation to initiate this programme and at the first meeting in late 1987 to establish a strategic plan, adopted the three components listed above as the top priorities. A Steering Committee (SC) was established to make recommendations to SAGE, the Scientific Advisory Group of Experts which through CDS, advises the Director-General of WHO. The Programme was advertised and in 1988, it was decided to commission research in

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.