The other finding which disturbs me is that spread of virus within the family was demonstrated in 13 (for type 1) and 17 (for type 3) out of 25 families. This is more frequent than I, for one, anticipated and raises a problem which I do not think was as thoroughly ventilated by the Committee as it might have been. The argument often put forward is that spread does not matter since the circulating viruses are less virulent than wild viruses. This is, I consider, not sound for two reasons. The first is that in a vaccination programme the amount of virus put into circulation in this way is vastly greater than the amount circulating naturally. Therefore, even if an increase in neurotropism occurs only occasionally, a considerable amount of neurotropic virus might be circulated artificially, perhaps many times the amount which is circulating naturally. The other point is that we do not yet know enough about how often an increase in neurotropism will take place nor how far it may go on repeated passage using different strains, in different age-groups, at different times of the year in different epidemiological situations. Practically all

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studies so far have been done in temperate zones during the "off season". Will the strains behave in the same way during the epidemic season, and what will happen in the tropics where the seasonal differences are not so clearly marked? Dick has already shown that the TN strain behaved differently in adults than in children even when both were non-immune. The results of the use of Sabin's strains in children are so far limited although I understand quite a lot more information will be available shortly.

We must I think accept that if familial spread is as common as shown in Minnesota we must expect extensive extrafamilial spread. The vaccine virus is therefore going to get loose in the community and we would in effect be "vaccinating" unintentionally many persons not included in the programme. If therefore we lay down certain standards for the vaccine we are going to administer deliberately, surely we should have the same standards for the "vaccine" which is going to spread unintentionally. I recognize that this may not be possible and that some relaxation of the standards may be necessary and may indeed eventually be justifiable, but I do not think we have reached the stage yet at which we can accept such a relaxation with confidence. At least I think this point should be carefully rediscussed.

In your letter to Dr. Rivers you contrast my concern about the Lederle strain with the "approval" of the Committee of Sabin's type 3 strain. It is my understanding that the Committee was careful to avoid giving approval to any individual strain; it laid down criteria which should be met by strains before they were considered acceptable for use on any considerable scale. I agree that at first sight that the results with Sabin's strain look similar to the results with the Lederle strain, however on closer examination it will be seen that that is not so. Sabin used much higher doses of virus, mostly between $10^7$ and $10^8$ whereas Cox used $10^6$. At $10^6.1$ or less only four of Sabin's strains produced paralysis, whereas 20 out of 41 of Cox's did. It is true that Sabin did not titrate all specimens but the small proportion of monkeys brought down by very high doses makes it seem unlikely that any would have come down with the lower dose. $\_\_\_\_\_\_\_\_\_\_\_\_\_$ and $\_\_\_\_\_\_\_\_\_\_\_\_$ are his only two bad results. These were titrated and account for 20 out of the 27 monkeys paralysed. Furthermore, although Sabin does not say so in the paper you quote, I think I am right in saying that he only passed the virus once in tissue culture. Nevertheless, I will admit that I am not as happy about his type 3 strain as I am about his types 1 and 2. A preliminary report from Professor Verlinde also shows some slight increase in intracerebral activity with this strain but not with the other two. I think we will need to watch this carefully although I do not think the evidence so far indicates that the strain will turn out to be unsuitable for more extensive use. It is merely an indication for caution. We should know more about this when the results of the several trials now in progress or being planned are available.

In my opinion we should now take steps to find a place suitable for a fairly large-scale trial of Sabin's strains with a view to starting in perhaps a year or two. The Lederle type 1 is not at present acceptable for such a trial and the evidence I have so far regarding the Lederle type 2 and 3 strains is quite inadequate. It will take some time to find a suitable place for the trial, to work out details, and to carry out preliminary surveys. By then we should have further results from current trials which will enable final details to be planned and a firm decision taken regarding Sabin's type 3 virus. If it should turn out to be unsuitable for large-scale use one could still go ahead with types 1 and 2 which look very promising.

Contd.
I will not at this time make any suggestions regarding the detailed organization of the proposed trial. I am in full agreement with your suggestion for an advisory committee and very much appreciate your suggestion that I should participate in the discussions.

However, apart from the considerations set out by the Expert Committee there are a few points which will have to be considered by the advisory committee.

1. What are they going to say if a field trial using (say) a type 1 virus which can spread is followed by a type 1 epidemic in the trial area or in an adjacent area? This possibility has to be faced. (It is of course one reason why it would be desirable if the vaccine virus had some readily recognized and fixed "marker".)

2. The possibility must also be faced that cases may occur by spread of virus from vaccinated subjects. Indeed, in my view, if any do occur it is probable that it will be in this way. This is a complex problem. One way of assessing this might be to feed only one child in each family. The occurrence of an excess of cases in the siblings of vaccinated children within one month of feeding would then be suspicious but it would of course still be impossible to be sure how many of these were due to stray wild viruses. The idea of vaccinating whole families or even communities while attractive in many ways actually sidesteps this issue.

3. In assessing the significance of feeding a large number of children without incident it will be necessary to know with some accuracy the immunity status of the population. This implies a fairly extensive preliminary survey. This takes time and should perhaps be planned at an early stage.

These are preliminary thoughts only and I look forward to discussing these problems with you, Sabin, Paul and others in due course.

Yours sincerely,

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Summary of conversations on attenuated poliovirus vaccine between Drs. Cox, Cabasso, Ottati, and Zink of Lederle Laboratories and Dr. Kaplan and myself.

Progress by Lederle Laboratories in developing strains of poliovirus of all three types of low virulence for monkeys was described and discussed.

Type 1 is the SM strain which has now been plaque purified five times (four times before the trial mentioned below) and is practically avirulent intracerebrally (IC) for monkeys, having caused paralysis in only one out of the last 119 monkeys inoculated. Intraspinally (IS) it is of low virulence, having paralysed 14 out of 50 monkeys in the last two series of tests.

Type 2 virus is derived from MEFl by passage in mouse brain, suckling hamsters, and chick embryo. It has now been passed a number of times in monkey-kidney tissue culture and has been plaqued 3 times. In the last test (after 2 plaques) it caused paralysis in one out of 30 monkeys IC and four out of 30 IS.

Type 3 is derived from the strain Fox PL49 and has been plaqued four times. In the last two tests it has caused paralysis in one out of 30 monkeys IC and none out of 12 IS.

Pools of quite considerable size of all three types are available. These have been subjected to extensive tests for safety, sterility, and the presence of other viruses. These tests were laid down in consultation with the National Institutes of Health.

The viruses have recently been subjected to further clinical trials under the control of Dr. Martins da Silva in Minnesota. Twenty-five infants born of mothers immunized with Salk vaccine, and therefore having maternal antibody, have been fed all three types in succession at the appropriate intervals. No symptoms resulted and almost all infants (one failure with type 1 virus and one with type 2 virus) were successfully infected and showed satisfactory antibody response. Evidence of familial spread of type 1 virus by virus isolation or antibody rise was found in 13 and of type 3 in 17 of the 25 families.

Studies on the characteristics of viruses isolated from the stools of subjects in this study are in progress and only clinical results of monkey tests with type 1 virus are as yet available. Histological examinations are not yet available. However, on the basis of the incidence of paralysis alone in monkeys given a standard dose of 10^5 TCD50 intracerebrally (from the third MKTC passage) there was irregular but unquestionable evidence of increased intracerebral virulence in some specimens. Taking all results together, 35 out of 164 monkeys were paralysed. The incidence of paralysis did not differ significantly in monkeys inoculated with virus isolated from the infants fed the virus, from that observed in monkeys inoculated with virus isolated from contacts (i.e. second human passage), the latter was actually slightly lower. The monkeys were used in groups of four for each stool. When paralysis occurred, as it did after inoculation of virus from 20 out of 41 stools tested, one or two out of the four monkeys were paralysed in a total of 16 instances and three or four out of four were paralysed in four instances. The possibility that wild poliovirus had been picked up in these latter instances could not be excluded.
My conclusion is that a definite increase in virulence was demonstrated after one human passage, but the viruses isolated were still of lower virulence than the great majority of naturally occurring strains, and that in these limited studies this change did not progress further after a second human passage. It is also evident that spread of virus, at least within a family, must be accepted as common.

Future plans were discussed. Plans are in hand for a further study in Minnesota consisting of feeding a random sample of 500 families, the whole family being fed at the same time. I pointed out that although such a procedure would eliminate the problem of passage within the family it would not answer the important question as to whether the viruses were likely to spread in the community, and that until there is evidence to the contrary it should be assumed that this will occur. It was suggested therefore that the possibility of studying this by obtaining stool samples and/or bloods from school contacts should be explored.

I further stressed that in my opinion the most important question to settle was whether the change observed in the virus was significant and whether it was likely to progress further towards full virulence on repeated passage. I pointed out that certain criteria had been laid down by the Expert Committee for the acceptability of a strain for human trials. The excreted virus in these studies often did not meet these criteria and yet it was evident that other people were being infected with these viruses. It would appear logical – even if not practicable – that the same criteria should be adopted for the excreted virus. However, at least it must be shown that the margin of safety is sufficient to make a limited relaxation of these criteria acceptable. It was suggested that this should be studied in Salk vaccinates (vaccinated three times), selecting the most virulent viruses isolated from stools after feeding and passing them serially through several human passages. It was also suggested that the least virulent strains isolated (as judged by spinal inoculation) should be similarly passed since this might lead to isolation of the most stable virus particles in this respect. Both these studies should be undertaken at a time when there is least chance of picking up stray wild polioviruses. It was agreed that these studies would be greatly facilitated if strains of type 1 and 3 with readily identified "markers" could be found, such as the hamster and chick embryo "marker" of this type 2 strain.

Mention was made of a proposal for a large-scale trial on upwards of a million individuals in Chile. I expressed my view strongly that we were not ready for such a large-scale trial. The above points must be cleared up first. Any accident now might set back progress for years. The only situation where I did feel that widespread use was already justified was in the face of a severe epidemic when these considerations are outweighed by the fact that no other action would be effective and there was a good chance that extensive use of a live virus vaccine might terminate an epidemic abruptly.

Dr. Cox undertook to keep me informed of progress.