Dear Albert,

Further to my letter of 7 January, I have now received some further data on tests of the SM type 1 strain in the Minnesota trial in addition to those published in the University of Minnesota Medical Bulletin. You may already have seen them but in case you have not I attach a copy. You will note that when the first tissue-culture passage was used at a titre of $10^6$ only 10 monkeys were brought down as compared with 25 when the third tissue-culture passage was used. In three instances no monkey was brought down whereas the same three viruses in their third passage had brought down 7 out of 12 monkeys. Only one monkey was brought down by a 10% extract of the original stool, but the titres used were low. Contrary to my expectation these results are somewhat more favourable than those originally reported. Considering only the first tissue-culture passage results on the stools which caused paralysis in the third passage in only two instances out of 10 was more than one monkey brought down at $10^6$TCD. In the absence of histological results bringing down one monkey is the minimal increase of virulence detectable. It may be said therefore that of these stools only two show more than minimal increase in virulence. These 10 stools are in fact all the stools which brought down more than one monkey in the original tests on the third tissue-culture passage, so that only two stools out of the 48 examined showed more than minimal increase in intracerebral pathogenicity; alternatively, two persons out of the 22 tested excreted virus showing more than the minimum detectable increase in intracerebral activity. These two persons are and in table 7 of da Silva's article.

If this is a fair interpretation of the results I do not think we can condemn this strain out of hand. My position as I indicated both in the memorandum of my conversations with Dr. Cox and in my letter to Dr. Soper is that this strain cannot as yet be considered to be acceptable for large-scale use, but that does not exclude the possibility that further tests might show it to be acceptable. I hear that further and more extensive tests are in progress in Minnesota and provided these tests include further adequate studies on the intracerebral activity of the viruses, preferably those isolated from both familial and extra-familial contacts (i.e. at least second passage), I shall keep an open mind until I see the results.

Professor A.B. Sabin
The Children's Hospital
Research Foundation
Elland Avenue and Bethesda
Cincinnati 29
Ohio
United States of America

Contd.
With regard to the other two Lederle strains, type 2 appears to be of greatly diminished infectivity and antigenicity. However, I wonder what would be the result of administering larger doses. I know that the Expert Committee specified that the virus used should be effective in doses of $10^5$ or less. At the time I had some reservations about this. The use of a larger dose would indeed increase the cost but even so it might still prove cheaper than the inactivated vaccine. I can see no objection other than cost to the use of a larger dose. In addition there are possibly certain advantages to this strain; there is a suggestion that it may only be transmitted with difficulty. I recognise that that may merely be a reflection of poor multiplication but it deserves further study as it is a very desirable characteristic. Also the strain has well defined markers which will make its study in the field much easier. With regard to type 3, the information so far available is insufficient but what there is is favourable so that further studies are indicated. I have explained this at some length to avoid any misunderstanding that WHO is committed to any particular strain.

There is another point which is causing me some anxiety and which I would like to clarify. Both WHO and the PASB, which has the double role as the WHO Regional Office for the Americas, are intergovernmental organizations. Both Organizations in planning or supporting work in any country are obliged to work through the national health authorities with whom the appropriate agreements defining both the obligations of the government and those of the Organizations are negotiated. The Organizations cannot allow themselves to be bound by conditions unless these have been the subject of negotiations between all the parties concerned. I stress this point because there are a number of health authorities which view plans for large-scale studies with alarm. WHO has therefore taken the only possible attitude that a decision regarding the conduct of trials in any country, including the approval of the strains to be used, is finally the responsibility of the national health authorities concerned and that WHO can support no action which has not been approved by the health authorities in consultation with WHO; the latter condition being necessary for the Organization to be able to ensure that the health authorities are fully informed of all relevant considerations, and for the Organization to be satisfied that the plan of operations is technically sound. Of course this does not preclude action being taken without WHO support, but if that support is needed this condition must be met.

As you know very well, I am most anxious to do all I can to assist progress in this field and regard the results you have obtained so far as being most promising. I hope that you will appreciate our position and enable us to co-operate in future studies to the best of our ability.

With kind regards,

Yours sincerely,

A.M.-M. Payne, M.D., M.R.C.P.
Chief
Section of Endemic-epidemic Diseases