December 4, 1957

Dr. Fred L. Soper, Director
Pan American Sanitary Bureau
1501 New Hampshire Avenue, N. W.,
Washington 6, D. C.

Dear Fred:

Thank you very much for your letter of 27 November. You asked me to check your comments on the tests for intracerebral neurotropism on the stool cultures derived from the volunteers who ingested the optimum plaque-purified attenuated Type 3 virus, and to forward any additional information that I may have.

The type 3 data to which you refer, contained in Table 15 of the July, 1957, J. A. M. A. paper, show that 28 of 137 monkeys inoculated intracerebrally with very large doses of the cultured virus (predominantly in the range of 10 million to 500 million tissue culture infective doses) exhibited paralysis. Upon analysis of these data it can be seen that 20 cultures from 11 individuals inoculated in 86 monkeys yielded either no paralysis or involved only an occasional monkey - the total number in this group being 10. Three cultures derived from the stools of 2 individuals yielded a higher incidence with 18 of 51. You will note that in each instance the inoculation of smaller amounts of
virus in the range of 10,000 to 100,000 tissue culture infective doses failed to produce paralysis. If you examine Table 6 in the same paper you will see that none of 21 monkeys inoculated with 10,000 to 100,000 infective doses of stool cultures derived from 7 volunteers, who ingested the same strain of Type 3 virus prior to plaque purification, exhibited paralysis.

Similar results were obtained by Dr. Paul and his associates with stool cultures derived from individuals who ingested an aliquot of the same Type 3 virus prior to plaque purification. Professor J. D. Verlinde of the Nederlands Instituut voor Präventive Geneeskunde, Leiden, Holland, early this year carried out studies with aliquots of the large lots of plaque purified viruses described in my July, 1957, J.A.M.A. paper. He carried out spinal and intracerebral tests for neurotropism in monkeys on the stool cultures derived from children and adults who ingested these viruses and on 26 November, 1957, wrote me as follows:

"A total of 39 excreted strains (14 type 1, 6 type 2 and 19 type 3) isolated from 21 vaccinated individuals have now been examined for neurotropism. None of the type 1 and none of the type 2 strains showed any increase of neurotropism. Three type 3 strains, recovered from 2 individuals, however, did produce paralysis not only in 4 out of 4 intraspinally inoculated cynomolgus monkeys, but
also in 2 out of 2 intracerebrally inoculated monkeys. One of these strains proved paralytogenic only after intracerebral inoculation of undiluted tissue culture fluid, the 2 other strains proved also paralytogenic in a dilution $10^{-1}$, but not in higher dilutions. One of these strains was recovered 15 days after oral administration, [while cultures from the same individual obtained] obtained 8 and 21 days after vaccination were inactive, and failed to produce paralysis even following intraspinal inoculation. The 2 other strains came from a child 16 and 21 days after vaccination, whereas [the virus cultured from the same child] 5 and 33 days after vaccination proved nonparalytogenic following intraspinal inoculation".

The latter observations of Verlinde on the failure of the more neurotropic virus particles to compete with the greater number of less neurotropic virus particles for persistence in the alimentary tract is of great importance and confirms observations that I had previously reported. Data of this kind indicate that the human alimentary tract does not preferentially select virus particles of greater neurotropism when they appear during the course of multiplication of highly attenuated strains - the selection is by the monkey nervous system during the course of testing for neurotropism (see discussion on p. 1594 in my paper in the J. A. M. A., Dec. 29, 1956, 62).
The significance of occasional monkeys exhibiting paralysis after intracerebral inoculation of very large doses (in the range of 1 million to 100 million) of attenuated polioviruses has been extensively investigated in my laboratory and is discussed in the paper entitled: "Characteristics and genetic potentialities of experimentally produced and naturally occurring variants of poliomyelitis virus", Ann. N. Y. Acad. Sci., 1955, 61, 924 - see especially table 7 on p. 933.

When the question is asked what are the pathogenic potentialities for man of a population of poliovirus particles in a stool which yields a culture that paralyzes monkeys intracerebrally inoculated with a million or more infective doses but not in the range of 10,000 to 100,000 infective doses, I can only say that maximal doses of such cultures inoculated intraspinally in chimpanzees have not produced paralysis.

In your letter to Dr. Rivers you indicated that recent tests in Minnesota on stools of children who were fed Koprowski's type 1 SM virus resulted in paralysis of 35 of 164 intracerebrally inoculated monkeys. In order to comment intelligently on these results one would have to know how much virus was actually injected and how the incidence of paralysis was distributed among different specimens. It can be said, however, that the type 1 virus that I have selected, did not yield such results either in my own tests or in those carried out by Verlinde. Dr. Koprowski told me that he has himself decided not to use the SM strain
in further tests and has substituted for it the "CHAT" strain about
which there are as yet only fragmentary data concerning the neuro-
tropism of the excreted virus. Thus, for the type 1 virus there is
no question that the special L Sc plaque strain that I selected is
superior to the SM strain. As regards the Type 3 virus, the special
plaque derivative that I am now using was selected after a long and
arduous study of many naturally occurring and experimentally modified
strains, and it is the best that has been obtained thus far.

I am enclosing the reprints you requested and I hope that
this information and discussion may be helpful to you.

With best wishes and kindest regards,

Sincerely yours,

Albert B. Sabin, M. D.

ABS: meh

cc: Dr. Thomas M. Rivers
    Prof. Dr. J. D. Verlinde
    Dr. John R. Paul