Dr. David N. Johnson  
Department of Public Health  
Brisbane,  
AUSTRALIA  

Dear Dr. Johnson:

Thank you very much for your letter of October 11, which came here at a time when I was away from Cincinnati. I was sorry to learn that you were hospitalized, and hope that by this time you are back on your job.

Since the publication of the work to which you made reference we have been engaged in extensive studies on a large number of other attenuated strains of poliomyelitis virus, especially those derived from the stools of healthy children during non-epidemic periods and without contact with known cases of poliomyelitis. The strains which are now under investigation in a new group of 48 human volunteers are much more highly attenuated than the ones with which the original studies were made. It is expected that at the end of this year we shall be able to select the optimum strain of each type for use in further studies on progressively larger numbers of human beings. It is possible that by spring of 1956 we shall have small experimental lots of each of the 3 types which will be thoroughly tested in experimental animals and available for further tests - in amounts that would be sufficient ultimately to carry out the studies up to 100,000 if that should be indicated. It is my hope that it may be possible to arrange for tests on groups of various sizes in different countries, using aliquots of the same lots of vaccine. I am leaving Cincinnati for Europe on November 1, and at that time I will discuss the possibility of such cooperative tests in a number of countries, as well as at a special WHO meeting on poliomyelitis vaccine, which will be held in Stockholm on November 21 to 25. I am also scheduled to meet with the Medical Research Council Committee on Poliomyelitis Vaccines in London on November 28 or 29.

In answer to your question about the assistance that I have been receiving from the National Foundation, I might say that up to the present I have had all the financial assistance that I required. I might, however, stress the word "financial" because in every other respect it can hardly have been said that the Foundation displayed any special interest in furthering this particular approach.

I should now like to answer some of the other questions you have posed. With regard to your question about the reason for the unusual virulence of the Mahoney strain currently used in the Salk vaccine, I will agree that its special capacity for multiplication in skin and muscle tissues in the body is an important factor in determining its unusual virulence when administered in the minutest
amounts. Not all extraneural tissues are the same, nor are all poliomyelitis viruses which are highly virulent after introduction directly into the nervous system capable of initiating paralytogenic infections after subcutaneous or intramuscular injections of minimal amounts. My own studies on chimpanzees lead me to the conviction that all poliomyelitis viruses possess the capacity for invasion along neural pathways. Whether or not this invasion is initiated from some particular extraneural site depends in large measure on the amount of virus that is available at the site and the capacity of a given strain to multiply locally is of considerable importance. After invasion is initiated, the subsequent course, in my opinion, depends on the capacity of the particular strain to multiply in neurons. If it multiplies very poorly, it will never get beyond the regional peripheral ganglia. If on the other hand, the particular strain can multiply extensively in the neurons, then it readily spreads further into the nervous system and the amount of damage that is produced again depends on the position of the virulence spectrum occupied by the particular strain.

I speak now of a virulence spectrum because the quantitative studies that I have carried out on a very large number of poliomyelitis strains indicate that there is a very large degree of variation among different strains. The available data strongly suggest that a very large number of genes are responsible for the character which determines multiplication and damage to primate neurons. Some strains apparently have a very small complement of these genes and others have a very large complement. I have also found that the genes which determine the capacity of a virus to multiply in primate neurons are entirely different from those which determine the capacity to multiply in the gut, and those which are responsible for multiplication in the gut are different from those responsible for multiplication in the skin and muscle, etc.

Viremia, in my opinion, is a reflection of the extent of multiplication in extraneural tissues. One can have quite extensive multiplication in the alimentary tract with invasion of the virus in the regional lymph nodes, with apparently such little spill over into the blood that no virus is detected by the usual tests. However, strains of virus which possess the capacity of multiplying extensively also in other extraneural tissues lead to more extensive viremia, and so strains can also vary to considerable degree as regards the amount of viremia that occurs, depending upon the extent of their multiplication in a variety of other tissues. In my opinion, the important determining factor actually is not whether or not the strain produces a little bit of viremia, but rather whether it produces a great deal of viremia, and ultimately from a practical point of view, the important question is what its capacity is to damage neurons after it reaches them. The ultimate choice, in my opinion, has to be made on the neurotropic status of a given strain. The fact that strains which are still moderately virulent for monkeys are completely without paralytogenic activity after direct intraspinal inoculation of the largest amounts in chimpanzees provides the real margin of safety in choosing attenuated strains for human use.
As regards your question as to how antibody is produced by strains which give rise to little or no viremia, the answer is that the lymph nodes are invaded and that appears to be quite enough for antibody formation.

With regard to plans which are under consideration for the preparation of a Salk-type vaccine in Australia, I need hardly stress the desirability not only of eliminating the currently virulent Mahoney strain, but also of using attenuated Type 2 and Type 3 strains. During the past summer I have distributed a number of attenuated strains of each type of differing residual neurotropic virulence for monkeys (strains which are completely avirulent for chimpanzees) to all the pharmaceutical houses engaged in the production of vaccine in this country, as well as to a number of investigators in foreign countries. From incomplete reports that I have received thus far, it would appear that they are quite suitable as antigens after formalinization. I would personally particularly recommend for Type 1 strains "P 2149" and "P 2226" which were originally derived from healthy children and have only minimal activity in monkeys by direct spinal inoculation (I should point out here that when unusually large inocula in doses of ten million TCD$_{50}$ or more are given intramuscularly - particularly when the inoculations are given into the hip muscles, deltoid, or pharyngeal muscles - that it is to all intents and purposes, similar to giving a somewhat smaller inoculum directly into the spinal cord). These strains multiply to unusually high titers (10$^8$ TCD$_{50}$ or more) in monkey kidney tissue culture and should be excellent substitutes for the virulent Mahoney virus. I have recently been informed by one of the pharmaceutical houses that one of these strains probably will be the substitute that they will use. I should also like to point out that I have a very excellent Type 2 attenuated strain that was derived from a healthy child and which has such minimal activity in the monkey that only when doses in the range of one million or more TCD$_{50}$ are put directly into the spinal cord that localized non-progressive paralysis is produced. Type 3 strains are also available. I should, of course, be glad to send these strains to Bazeley as I have to others - if he should want them.

With all good wishes and kindest personal regards,

Sincerely yours,

Albert B. Sabin, M. D.