February 6, 1952

Dr. Pearce Bailey, Director
National Institute of Neurological Diseases and Blindness
National Institutes of Health
Bethesda 14, Maryland

Dear Dr. Bailey:

In my letter of January 11, 1952, I promised to send you within about two weeks a reply to your request for a statement on the needs for research in infectious diseases of the nervous system. I regret very much that a number of events have interfered with my resolve to give the matter a good deal of thought, but since I do not want to delay any longer, I will send you my comments on this subject without having given to it as much thought as I should like.

**Question 1** — "Benefits derived from research in infectious diseases of the nervous system during the last ten years?"

In my opinion the following are at least among the most important contributions:

a) The beneficial results obtained from the application of antibiotics to bacterial infections of the nervous system including tuberculous meningitis.

b) Advances in our knowledge of the arthropod-borne viral encephalitides — important new knowledge on the natural history of these infections even though much more remains to be learned; development of diagnostic methods; discovery of hemagglutination as a function of many of these viruses with the consequent development of improved rapid methods for diagnosis and epidemiologic survey.

c) Advances in our knowledge of poliomyelitis — important new information on the nature of poliomyelitis infection in man, behavior of the virus in nature, immunological classification of poliomyelitis viruses; new information on behavior of different strains of virus in various experimental animals, discovery of the cytopathogenic properties of poliomyelitis viruses for non-nervous tissues and tissue cultures.
d) Demonstration of the danger for the fetus of certain mild viral infections in the pregnant mother.

e) Demonstration of the role of congenital toxoplasmosis as a cause of cerebral and ocular damage; also development of new quantitative and reliable diagnostic methods for this infection.

Questions 2, 3, 4: "Important trends in current research, new fields to be explored and beneficial results that might reasonably be expected from these?"

I should like to deal with these three questions under one heading. In my opinion the most important infectious disease of the nervous system at the present time, both from the point of view of incidence and worldwide distribution, is unquestionably Poliomyelitis. Although the existence of the National Foundation for Infantile Paralysis in the U.S. has greatly stimulated research on this disease, it is my opinion that only a fraction of what needs to be done is being done. The National Foundation spends roughly about $1-1/2 million a year for research, not because more money could not be allocated from the $25-30 million that is collected yearly but rather because that is all the money that is being requested by the investigators in laboratories currently engaged in this work in the U.S. I personally believe that much more work needs to be done and that this could be accomplished by a more organized and coordinated attack on the various problems in addition to the current laissez-faire approach of individual investigators. What one would like to have in poliomyelitis is a simple test for the detection of current as well as past infection with the various types of poliomyelitis virus, and a method of preventing the paralytic consequences of poliomyelitis without affecting the inapparent or mild infections which lead to lifelong immunity. An alternative to the latter goal would, of course, be the discovery of a method of vaccination which could be used as effectively as that against smallpox or yellow fever. These would be the achievements that one might expect from a more concerted attack on poliomyelitis in the forthcoming years.

From the point of view of frequency of occurrence, I am inclined to regard the Toxic Encephalopathies as being next to poliomyelitis in importance among the diseases of the nervous system caused primarily or secondarily by infectious agents. I would define "toxic encephalopathy" as involvement of the central nervous system during the course of various bacterial infections elsewhere in the body in which the pathological changes in the nervous system are not associated with inflammatory reactions. I realize that this definition may be regarded by some as arbitrary, but I have found it clinically useful for the past twelve years in observing such encephalopathies in children. During life such a
patient reveals no pleocytosis and postmortem one can find no inflammatory reaction even to grossly apparent degenerative changes of the nervous tissue. It seems to me that, particularly in children, toxic encephalopathy, when it lasts more than a brief time, is probably responsible for a great deal of residual cerebral damage. As far as I know, there are no studies in progress on this most important and frequent disease of the nervous system. I do not know whether a special study directed at the neurotoxic properties of the bacterial flora that may be recovered from such patients (either from the respiratory tract, enteric tract, or other focus that may exhibit evidence of bacterial infection during the course of toxic encephalopathy) would yield the desired information, but I would regard such a study as highly worthwhile. If this hypothesis of the etiology of the vast majority of toxic encephalopathies can be established, it may provide a means for diminishing serious consequences of this disease, particularly in childhood.

The Arthropod-borne Viral Encephalitides, because of their limited geographic distribution and relatively infrequent incidence of large-scale outbreaks, are in my opinion probably not as important as a cause of disease of the central nervous system as the toxic encephalopathies. However, they do present an important problem, and I believe that further studies on the natural history of these infections, particularly with regard to the ultimate reservoir of these viruses in nature, chemotherapy, serum prophylaxis during epidemics are problems which deserve further intensive study. The information derived from such studies may be expected to be helpful in preventing the occurrence of large-scale epidemics as well as to provide us with the best means of dealing with an epidemic when it comes.

From the point of view of incidence, I don't know exactly where to put the Demyelinating and Neurotoxic Encephalitides — In this category I include those diseases of the central nervous system which are secondary to viral infection elsewhere in the body as, for example, after measles, chickenpox, etc. Here the damage to the nervous system while also being secondary, as in the case of the toxic encephalopathies, is nevertheless invariably associated with an inflammatory response which is detectable by pleocytosis during life and an inflammatory reaction postmortem. I add the word "neurotoxic" to "demyelinating" because it is my impression that acute degenerative changes of the neurons are not infrequently associated with the other changes which lead to perivascular demyelination. I hesitate to mention any specific approach to learning more about this type of disease of the nervous system, but I would like to see studies along this line encouraged.

Another achievement that I would regard as practically important would be the preparation of a Rabies Vaccine that can be used in human beings without fear of demyelinating encephalitis. I would also encourage studies which would provide more effective prophylaxis than is currently available in those cases of rabies which have a relatively
short incubation period.

Among the diseases of the nervous system which are secondary to bacterial infections elsewhere in the body, I would strongly consider Acute Infectious Polyneuritis (Guillain-Barré syndrome). The type of study which I suggested on toxic encephalopathy may perhaps also be pursued profitably in this particular syndrome.

Among the Congenital Infections which are responsible for Cerebral and Ocular Damage, those caused by the viruses such as German measles and by the protozoan parasite, Toxoplasma, continue to be a problem although the incidence of these infections is not very high. At the moment, I can think of no special study other than those directed toward a better understanding of the etiological agents themselves. My own studies along these lines have aroused my interest in a non-inflammatory disease which produces cerebral and ocular damage. The clinical and pathological findings are chiefly those of chorioretinopathy and defective cerebral development, although there is also a smaller group in which there are destructive changes in the brain leading to calcification. Although multiple cases have been encountered among siblings, the defective development does not appear to be on a genetic basis. I have a suspicion that it may be related to something else which may damage the nervous system during certain periods of embryonic development. These patients usually present themselves as suspects of congenital toxoplasmosis and they can be separated from this congenital infectious disease by appropriate serological tests.

I hope you will excuse this rambling reply to the questions you asked and that it may nevertheless contain something that may be helpful to you in planning a program of study on the diseases of the nervous system which primarily or secondarily are due to infectious agents.

With all good wishes,

Sincerely yours,

[Signature]

Albert E. Sabin, M. D.