January 18, 1954

Dr. Joseph Garland
Editor, The New England Journal of Medicine
8 Fenway
Boston 15, Massachusetts

Dear Dr. Garland:

Enclosed you find the editorial I wrote on the "Present status of research on vaccination against poliomyelitis". If the editors of the New England Journal of Medicine concur in the sentiments expressed, I should be delighted to have you use as much or as little as you may see fit. I would also assume that my part in writing this editorial would remain confidential with the editors of the Journal.

I shall look forward to hearing what your decision may be.

Sincerely yours,

Albert B. Sabin, M.D.

ABS/jcs

Encl: editorial.
Present Status of Research on Vaccination Against Poliomyelitis

Research on vaccination against poliomyelitis has entered its most promising phase during the past 2 years as a result of the discoveries of Enders, Weller, and Robbins which demonstrated that all 3 types of poliomyelitis virus can be propagated in cultures of nonnervous tissue and that the presence or absence of virus can be established by cytopathogenic effects in vitro. There are two main approaches to the problem: 1) development of a 'killed virus' vaccine that is antigenic in small enough dosage to permit its manufacture for many millions of individuals, and at the same time sufficiently stable and devoid of dangerous side-effects to make it practical, and 2) to find or develop avirulent (nonparalyzing) variants of the 3 immunologic types of virus which conceivably might prove as effective against poliomyelitis as the 17 D variant is against yellow fever or vaccinia against smallpox. The final answer as to whether any poliomyelitis vaccine is really effective in preventing the natural disease can come only from carefully controlled experiments on tens or hundreds of thousands of children, and public health officers and physicians all over the country have recently been asked to cooperate in such an experiment by The National Foundation for Infantile Paralysis. Since human experiments on so large a scale do not lend themselves to frequent repetition, it is highly desirable to seek a dispassionate analysis of the scientific data on which such an experiment must be based as well as to consider the consequences of a successful or unsuccessful outcome.

Although no new scientific discoveries are required to determine whether or not a suitable "killed virus" vaccine can be developed for a definitive human experiment, a tremendous amount of development work by quantitative standardized...
assay methods must be carried out before one can be certain that results obtained in small exploratory tests are sufficiently reproducible to warrant the performance of the larger tests. Excellent work along these lines has been performed by Doctor Salk and his associates, but we have not seen any publications of systematic work on this phase of the problem from any other laboratory.

From Salk's first preliminary report², it appeared that 0.3 cc to 1 cc of formalinized tissue culture fluid, administered with adjuvants in one or more doses, effectively boosted the level of antibody in children who already possessed some as a result of previous infection with one or more types of poliomyelitis virus, but no evidence was presented that this amount of vaccine with adjuvant could produce antibodies for the important Type 1 virus (the type responsible for almost all epidemics) in children who had no antibody to begin with. In the second preliminary report³, evidence is presented that 9 children without antibody for any of the 3 types of virus developed antibody for all 3 types in titers of 1:4 or more after 3 intramuscular injections of 1 cc of aqueous vaccine without adjuvant at weekly intervals. In another test with 0.3 cc of aqueous vaccine given intracutaneously 3 times at weekly intervals, 2 of the 6 children tested failed to develop antibody for the Type 2 virus, while all developed antibody for Types 1 and 3. Whether or not the small amounts of antibody developing after aqueous vaccine are as effective against other strains as for those used in the vaccines is not known, nor is it known whether the antibody persists for as long as 6 to 8 months. These findings are, nevertheless, most encouraging, particularly if it can be shown that they can be regularly obtained with vaccines having a certain minimum standard of antigenic potency as determined by a reproducible method of assay.

No data have as yet been published on any method of assay or on stability of
stored vaccines. The preliminary tests on children were all made with vaccines inactivated by a 1:250 dilution of formalin at 10°C, while the ones that are to be used in the projected human experiment are to be inactivated by a 1:4,000 dilution of formalin at 35°C, and we have seen no data to show that they will still be of adequate potency several months after preparation at the time they will have to be used. Concern has also been expressed about the use of the virulent Mahoney strain of virus in the vaccine because minimal amounts of it produce paralysis more readily by the intramuscular route than by the intracerebral route, and a safety test even on 50 monkeys does not eliminate the possibility that 1 in 1000 or 1 in 10,000 might not be paralyzed. There are other Type 1 strains of virus which do not possess this property that could undoubtedly be substituted in vaccines that are to be used in hundreds of thousands.

The projected vaccines are to be made from the kidneys of rhesus monkeys, which of necessity retain a certain number of red cells, and one would want to make certain that repeated injections will not sensitize Rh negative girls to a point where the danger to Rh positive offspring they might bear will not become much greater than it is ordinarily. We would like to see the results of such tests as well as of tests for potential nephrotoxic effects, before proceeding with a mass trial on hundreds of thousands. We are in sympathy with Doctor Salk's recent statement: "We do not want to allow any distortion of the fact that we are still actively in the stage of clinical investigation; and that this work must be continued, but it must be continued gradually and cautiously". It also seems to us that systematic work on so important a problem should be pursued in more than one laboratory, and we are somewhat surprised that the fine
teamwork, which The National Foundation used so successfully to help obtain a conclusive answer on the number of types of poliomyelitis virus, has not been utilized in this most important development.

The potential development of a vaccine utilizing living, avirulent strains of poliomyelitis virus has been advanced by Sabin's recent discovery that all 3 immunologic types of poliomyelitis virus could be converted from virulent to avirulent forms by special methods of cultivation in nonnervous tissue. The data he presented at the December 1953 meeting of the New England Pediatric Society indicated that the work had progressed sufficiently to warrant the extensive laboratory studies which must precede any tests on human beings. It seems to us that the prospects for finding an effective and practicable method of vaccination against poliomyelitis look better now than ever before, but there may be considerable wisdom in making haste slowly.

References


