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Dear Aims:

This is in reply to your inquiry about my reaction to the letter addressed to the Committee on the Control of Infectious Diseases of the American Academy of Pediatrics by Dr. C. Henry Kempe on the subject of the proposed mass vaccination trial of a formalinized poliomyelitis vaccine. I have not discussed this matter with Dr. Kempe at any time, but I completely agree with his conclusion: "that the formalin-inactivated vaccine is insufficiently tested for mass trial, potentially unsafe, of undetermined potency, and of undetermined stability". The data supplied by Dr. Kempe in support of this conclusion are sound and valid, except in a few minor details. For example, I had nothing to do with the decision not to use an "adjuvant-type" vaccine, and my own information is that a 1:4,000 rather than a 1:8,000 dilution of formalin is being used for inactivation of the virus.

I am fully sympathetic with those people in the National Foundation for Infantile Paralysis who believe that tests for the effectiveness of a poliomyelitis vaccine should not be postponed until the best possible vaccine has been prepared, but rather that it should be done as soon as an effective and safe vaccine has been prepared. The real question in my mind, therefore, is whether or not the currently available data indicate that such has been achieved. It becomes immediately obvious that a decision must rest on the definition of "effective" and "safe".

My criteria for a minimally effective formalinized poliomyelitis vaccine are as follows:

1. The dose required to produce antibody for all 3 types of poliomyelitis virus, in children possessing none prior to inoculation, must be small enough to permit manufacture for tens of millions.

2. The induced antibody should persist for at least 6-8 months.

3. It must be demonstrated by a suitable laboratory assay method that:
   a. different lots of vaccine prepared by the proposed procedure possess similar antigenic potency, and
b. the antigenic potency persists without significant loss over a practicable period of storage.

There are at the present time no published data on the vaccine proposed for mass trial. It is, nevertheless, a fact, as Dr. Kempe points out, that the data presented by Dr. Salk at the last meeting of the American Academy of Pediatrics, contained tests on only a small number of children who received the proposed 3 doses of aqueous formalinized vaccine. I do not know whether or not the vaccine used in these preliminary tests was inactivated according to the latest procedure. The point, however, is that the response in the children possessing no antibody prior to inoculation was minimal and not uniform -- in fact it could be regarded as being borderline. Since the antigenic potency of formalinized vaccines in general may vary from lot to lot, and since persistence of this antigenic potency on storage is also influenced by the procedure of inactivation, one cannot predict the effectiveness of different lots of vaccines when one is working with preparations of borderline potency in the selected dosage. No laboratory method of assay has as yet been developed or standardized to the best of my knowledge, and I have seen no data on variations in potency or stability on storage. It is also important, in the case of preparations of borderline potency, to show that antibody has developed for strains other than those used in the preparation of the vaccine. I am sure that such data will become available in due time, perhaps even before February 1954 -- but until I see the results I cannot tell whether or not the time has come for a mass trial from the point of view of effectiveness.

The problem of producing a formalinized vaccine on a large scale from monkey kidneys is deserving of further consideration. One may conservatively estimate that the kidneys of approximately 250,000 monkeys will be required to produce vaccine for 50 million children. It is possible that the muscle tissue may be used, or that with more antigenic strains of virus the effective dose may not be so large. All this remains to be investigated, and in my opinion a "mass trial" should be carried out only with material that can be "mass-produced".

My criteria for safety of a formalinized poliomyelitis vaccine are as follows:

1. The strains of virus used in such a vaccine must not possess the property of producing paralysis after peripheral inoculation of minimal amounts.

(The virulent Mahoney strain used for the preparation of the proposed vaccine possesses this property. I do not regard the intracerebral injection of 10 monkeys as an adequate test for inactivation of virus of the virulent Mahoney type, because monkeys develop paralysis more readily after intramuscular injection than after intracerebral injection of minimal amounts. Besides with a virus of this
type, 50 monkeys may show nothing but 1 child per 1000 inoculated
may develop paralysis. This may not happen with some preparations
but may happen with others, because inactivation with formalin does
not always proceed to the same extent. Any vaccine prepared with
such a strain of virus is potentially dangerous. There are other
Type I poliomyelitis viruses which do not possess this unfortunate
property. In my opinion, a mass trial should be postponed until
suitable substitute strains have been investigated.)

2. It must be shown that repeated injections of formalinized monkey
kidney extract shall not:

a. produce "Rh" antibodies (all the red cells are not washed out
of the kidneys, and the kidneys are disintegrated as a result
of virus action in tissue culture), or

b. produce anaphylactic or nephrotoxic reactions, particularly
when the injections are repeated after the interval of one year.

Let me end this comment by expressing the belief that a safe and effective
vaccine for poliomyelitis, of one kind or another, will become available -- but
we have only just begun to learn and it would be wise to make haste slowly. I
heartily endorse the resolution of the Academy of Pediatrics which begins with the
words: "When and as it becomes possible to extend, etc., etc."; the point of this
letter is that the time is not yet -- perhaps soon, but not yet.

Sincerely yours,

Albert B. Sabin, M.D.