October 7, 1959

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Dear John:

Thank you very much for your letter of October 5 and the copy of the protocol for the study of live poliovirus vaccine in newborn infants. I think that this is an excellent protocol and that a great deal of new and important information should become available as a result of your proposed studies. Assuming that the various dilutions indicated in your protocol have reference to a dose which would be given in a 1 ml. quantity (and I think that less than that would not be advisable) I calculated that the minimal amounts of type 1 vaccine that you will require will be 310 ml, and of the type 2 and type 3 vaccines about 162 ml. Accordingly I would say that you should have on hand at least 350 ml. of type 1 and 200 ml. of type 2 and type 3. I would appreciate it very much if you could check on my calculations and let me know how much of each type additional vaccine you will require based on what you may now have on hand and the approximately 100 ml. of type 3 vaccine that I sent to Henry Gelfand on Sept. 28th. In view of the fact that the administration of the vaccine is in New Orleans I cannot understand why Gelfand asked me to send the vaccine to him at Chamblee. I would appreciate it very much if you could let me know whether the additional amounts of vaccine that you will require should be sent directly to New Orleans or for some, to me, incomprehensible reason first to Gelfand at Chamblee.

I would like at this time to mention here some thoughts that have been going through my mind recently with regard to certain factors that may influence the multiplication of poliovirus vaccine in
newborn children:

1) Role of colostrum and breast feeding. - You may recall that in 1950 I carried out extensive studies on the polio antibody content of human colostrum and breast milk. My findings, in brief, were that only mothers who had neutralizing antibodies for a given type of poliovirus in their blood produced antibody that was demonstrable in the colostrum and breast milk. The amount of antibody in the colostrum and breast milk was not proportionable to that in the serum and the results indicated that the antibody was being produced in the breast itself together with the other milk proteins. At that time I also carried out tests in cynomolgus monkeys on the effect of feeding human milk of known antibody content on orally induced infection with virulent homotypic poliovirus. These studies on a fairly large number of monkeys showed that the daily ingestion of 60 ml. of human milk had no effect on the infective and paralytogenic capacity of the poliovirus given by mouth - as a matter of fact the incidence of paralysis was higher than in the control monkeys which received only water instead of milk. At that time I thought that it meant that this amount of antibody ingested in milk was without effect but on the basis of more recent information I am not prepared to accept this conclusion because most of the infection with poliovirus in cynomolgus monkeys as in chimpanzees occurs in the posterior pharyngeal wall rather than in the intestinal tract as it does in human beings. Accordingly I am not at all sure that the ingestion of large amounts of antibody containing milk by infants may not in some instances modify the extent of or perhaps even prevent multiplication of the virus in the intestinal tract. That the ingestion of antibody containing milk does not by itself account for the failure of some newborn children to develop antibody after receiving the vaccine on the day of birth is evident from the data of Contreras. An examination of his protocols showed that the mothers of 3 infants who failed to develop antibody also were without homotypic antibody in the blood and accordingly it is most unlikely that their colostrum or milk had any neutralizing antibody for the virus. At any rate I think it would be
helpful if in your study you could have information on whether or not the children were breast fed or bottle fed.

2) **Role of gastric acidity.** - It is known that below about pH 2.5 poliovirus is quickly destroyed. In my early studies on monkeys there was strong suggestive evidence that the preliminary feeding of milk or other substances that would lower the gastric acidity increased the incidence of infection. Accordingly I was most interested to find in the literature that within minutes or a few hours after birth the gastric acidity in infants becomes very high. In 260 infants examined between 5 and 24 hours after birth, Huhtikangas (Untersuchungen über die Reaktion des Mageninhalts bei Neugeborenen, Acta. Soc. med. fenn. duodecim. 24:1, 1936) found the average pH of gastric contents to be 1.45, which expressed in terms of titration, is equivalent to a free agent of 36 ml. N/10 HCl. In commenting on these observations Clement Smith (The Physiology of the Newborn Infant, second edition, page 189) writes as follows: "Thus it appears that observations regarding gastric acidity in the newborn period must be evaluated with regard to the number of hours (if not of minutes) after birth, at which samples are obtained. A more or less neutral reaction within the first few minutes is rapidly replaced by a strikingly acid one." This leads me to wonder as to whether the high gastric acidity in most infants shortly after birth may not be one of the factors which may reduce the efficacy of orally administered vaccine.

This leads me to consider the need for investigating still another method of immunizing newborn children which would be simple and at the same time not be affected by gastric acidity. I have reference to swabbing the vaccine directly on the posterior pharyngeal wall. A number of years ago I tested this procedure with all 3 types of poliovirus in 10 young adults without homotypic antibody (3 for type 1, 4 for type 2 and 3 for type 3). I dipped an absorbent cotton swab in the undiluted culture fluid and rubbed the
swab directly over the tonsillar faucies and posterior pharyngeal wall. Multiplication of the virus in the throat occurred in each instance and virus was also excreted in the stools. The only possible objection to this that I can see is that in infants with maternally transmitted antibody the secretions on the posterior pharyngeal wall may have antibody. However, it is possible that rubbing the swab with virus directly on the tissue may overcome this potential difficulty. At any rate I believe that it is important to include at least a small group of infants in which this procedure would be tried with type 1 vaccine. It seems to me that if this should work it would be a much more potentially practical procedure than that mentioned in group 4 of your protocol involving the use of a feeding tube. Would you consider adding a group of at least 15 infants in which the vaccine is swabbed on the posterior pharyngeal wall on 3 consecutive days?

You asked me if I had any information on infants known to have been infected in the first few days of life. As you know from the correspondence that has been exchanged, the Contreras data with type 1 vaccine were all obtained in infants who received 1 ml. of diluted vaccine on the day of birth. They also received type 3 a month later and type 2 a month after that. Antibody production was determined only on specimens obtained 1 month after the administration of the type 2 vaccine or about 3 to 4 months after the type 1 was given on the day of birth. As you know about 50 to 60% clearly developed antibody. As regards those that failed to develop antibody there is no knowledge whether or not the virus actually multiplied in them but it may be pointed out that the failure to develop antibody is not directly related to the fact that the type 1 vaccine was given on the day of birth, because 13 out of 41 also failed to respond to the type 3 vaccine that was given one month later and about 50% also failed to respond to the type 2 which was given 2 months after birth. As far as I know Contreras has not fed any of these infants subsequently. However, you know that in tests reported by Koprowski he found that infants who failed to respond to the usual dose during the first few weeks after birth did respond when they were fed a similar or larger dose several months after birth. I intend to write to Contreras to inquire whether he can locate any of the

* actually some within 72 hours.
infants that failed to respond and test their present antibody status and if still negative determine the effect of giving them vaccine again. With regard to your last question I have no information on the sero-response in the few instances of congenitally acquired infection.

With best wishes and kindest regards.

Sincerely yours,

Albert B. Sabin, M. D.

ABS: meh

cc: Dr. Henry M. Gelfand
    Dr. Thomas M. Rivers
    Dr. Krugman