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Dear Dr. Sabin:

Because of my interest in you and in the subject matter, I have read with great care your manuscript entitled "Epidemiologic Patterns of Poliomyelitis in Different Parts of the World." It is a comprehensive statement and brings together in an effective manner a large number of observations from different parts of the world for comparison and interpretation. Please allow me to express my admiration too for the mechanical perfection of the presentation. You must have a valuable assistant in the one who does your tables and graphs.

I have taken your invitation to comment upon the manuscript seriously, and will undertake to state my criticisms quite frankly for what they are worth to you. First, let me make some general comments, then I will be more specific as to the questions that might be asked you regarding statements in the text.

A large part of the paper is devoted to a consideration of the validity of the theory of latent immunization. Nowhere in the text is there a statement of what is meant by the theory of latent immunization. As I understand the implication, the theory is that the age distribution of the disease, poliomyelitis, is determined by age susceptibility, and age distribution of susceptibility is the result of previous experience with the specific antigen, that is, previous infection, either clinical or subclinical. The theory also assumes that there is universal susceptibility of all individuals to infection with the poliomyelitis virus. Is this your conception of what is meant by the theory? If so, who is it that claims that such a theory is adequate for the explanation for the differences in age distribution of poliomyelitis in various places and at different times?
If I were stating a hypothesis on which to base the interpretation of age distribution pattern, it would be somewhat as follows: After the first few months of life, during which the infant is protected either by 1) the maternal immunity, or possibly by 2) the lack of maturity of susceptible tissues, there is universal susceptibility to infection with poliomyelitis virus. Immunity is acquired by contact with a specific antigen either through clinically recognized or subclinical attacks. The durability of this immunity is unknown, but since the disease becomes progressively more rare with advancing age, and there is no reason to believe that the older ages are not equally exposed to the infection, it would appear that the immunity acquired in early life was of a durable nature. Thus, the age susceptibility pattern of a community of human beings is the result of previous experience. For example, if the virus has been absent from the community for a long time, one would expect maximum susceptibility in the younger age groups but as the older age groups were approached there would still be a considerable proportion of susceptibles left over from the last experience.

The age distribution pattern of cases of clinical poliomyelitis during a brief period of time (i.e., epidemic period) is determined not only by the age susceptibility pattern, but also by the circumstances of exposure to infection, whatever they may be. At the present time we know very little about the conditions which are required for transmission of the virus from one individual to another. It seems highly probable that they involve the very intimate association which exists in a household or among children at play, rather than the casual extra-mural contacts such as exist at large in the community and affect the travelling public. (This inference is drawn from observations upon the rate of spread and its slow radial character). There is considerable doubt at present as to whether the kind of contact which affects children at school is particularly hazardous or not. It is entirely possible that adults, such as soldiers living in barracks, may at times suffer a higher exposure rate than they normally do under the scattered conditions of civil life. Temperature and humidity may play an important role in the extra-human time of survival of the virus. It suffices to point out that there are (unknown) circumstances which are
relatively favorable or unfavorable to rapid and widespread dissemination of the virus of poliomyelitis in a community of people. The point that I wish to emphasize is that it is generally accepted by epidemiologists that the circumstances of exposure (contact rate between infected disseminators and non-infected susceptibles) are just as important as age susceptibility in determining the age distribution pattern of clinical cases. Both have to be taken into consideration in the interpretation of data from any epidemic or from endemic prevalence. If you accepted these premises instead of your "theory of latent immunization" considerable revision would be necessary.

In any event, I am enclosing a memorandum of comments which occurred to me as I read your text, for what they are worth to you. I question the validity of paragraphs 7, 8 and 9 in your summary. Paragraph 10 is simply a statement to the effect that we need to know more about the circumstances of effective exposure in different communities and countries. Granted!! There is no argument about that!!

As stated in the opening paragraph, you have brought together some interesting data, and your comments indicate that the epidemiology of this disease still requires considerable elucidation before these data can be interpreted satisfactorily. As I understand the plan, it is proposed that all of these papers which are to be read at the International Conference are to be published in the Proceedings. If in addition to this you wish to submit your paper for publication in the AMERICAN JOURNAL OF HYGIENE, I will be glad to forward it to the Managing Editor for consideration. I shall await your further advice, since I am doubtful as to whether it would be acceptable under the circumstances.

With cordial personal regards,

Sincerely yours,

Kenneth F. Maxcy, M.D.
"paralytic poliomyelitis is but one part of the clinical spectrum." If one substituted for paralytic poliomyelitis a clinically recognized attack, the statement would hold for all infectious diseases with the possible exception of measles. The important point is the ratio between the frequency of infections which are clinically manifest and those which are inapparent. We are at the present unable to measure this ratio accurately.

Page 3. Ratio between number of deaths and number of paralytic cases in Cincinnati, Ohio in 1911 and 1947. This comparison would be valid only if it could be shown that the reporting of paralytic poliomyelitis was equally complete in the two studies. It is entirely possible that in 1947 there was more accurate clinical diagnosis of paralytic poliomyelitis and better reporting of the disease than there was in 1911. To base a case-fatality rate upon reported paralytic cases is hazardous, except in those situations, such as the Army, where you are sure that the enumerator is complete.

Page 4, line 14, infection was less in rural areas. This should read exposure to infection was less widely spread in rural areas, and, accordingly, infants and young children were more likely to escape infection until they had reached an older age group.
Page 4, line 16, It would be difficult to prove that "the generally greater total incidence of the disease in rural areas, especially during the first twenty years of this century." Have you any evidence to support this statement? It would be necessary to show that when children had reached the age of twenty, a higher proportion gave a history of having had a clinical attack among those who had lived in rural areas than among those who had lived in urban areas. I have been unable to find any data which demonstrate this fact.

Page 5, line 11, "despite the rarity of the disease" insert before disease paralytic.

Page 6, "the concept of latent immunization." This is the first time this term is used. In conclusion No. 9, the statement is made that "hypotheses which are based on the concept of latent immunization, etc." There is need of defining this term more accurately.

Page 6, line 8, Table V is unnecessary. Anyone who is familiar with the methods of epidemiology knows that it is unsafe to draw inferences with regard to changes in the percentage age distribution of a disease without reference to changes in the age composition of a population. It is generally accepted that age-specific attack rates are necessary for comparisons of this kind.

Insert page 6, second paragraph: It is questionable
whether the evidence presented from the three largest epidemics in New York City in 1916, 1931 and 1944, can justify the generalization that the percentage distribution of cases revealed a continuing change in the age selection pattern. The age distribution of an epidemic may or may not be representative of the age distribution pattern of the disease in this population over a period of time. In other words, you have illustrated your point by three samples. You are not at all sure that the three samples are equally valid. A single epidemic of poliomyelitis, as you abundantly prove in your later text, may have a peculiar age distribution.

Page 8, Chart 4: Comparison of the 1931 epidemic in New York with the 1911-13 Swedish urban epidemics. Similar age-specific attack rates. Last sentence in this paragraph. "This is chiefly to indicate that a pattern which appears in one part of the world may not appear in another until many years later." If one looks far enough and long enough one might find age distribution patterns which are quite similar or quite different, in the same country or in different countries.

Page 9, fifth line from bottom: "The high resistance of the first six months of life and the relative resistance in the next six months of life are well known and always contribute a part to lowering the total attack rates of the first five years of life." I do not believe that anyone can state at the present time whether the relatively low attack rate under six months is due to high resistance or less exposure, or both.
Page 11, sixth line from the bottom: The variation in age incidence is always determined by both factors, i.e., age-specific immunity status plus age-specific exposure. As a disease agent flows through a population it is not surprising to find that the age pattern varies. Your data on the change in the age distribution during the epidemic in Berlin are most interesting. One might also suggest that the explanation is that the epidemic tends to originate in the most susceptible portion of the population and as it develops, reaches the more resistant groups, exposure being widespread and general.

Page 12, 3 lines from bottom: "It is difficult if not actually impossible to explain such data on the basis of increasing latent immunization with increasing age. The only proviso being that the rate is slower in the rural areas than in the cities." The same comment as previously, the age selection is the result of two factors, immunity and exposure, according to age. One must furthermore take into account the past history of poliomyelitis in a particular community. It is entirely possible that in such rural areas as are mentioned here that during a previous epidemic a large proportion of the younger age groups were exposed to infection and became immunized, whereas a considerable proportion of the older age groups escaped infection. Accordingly, when this epidemic began there was a proportionately greater susceptibility in the older age groups. Or the circumstances surrounding the epidemic may have been such that the older age groups were exposed to a greater extent than the younger age groups.
Page 13, 8 lines from bottom: "Again we cannot escape the possibility that density of population may be only incidental to other as yet unknown factors which affect the incidence of this disease." Correlation of attack rates with density of population can only reveal indirect association. As pointed out previously, the age pattern of cases of paralytic poliomyelitis would be determined by the past history of the disease in a particular locality and the circumstances of exposure during the particular epidemic under consideration. Such observations as you have made here certainly do not obviate the necessity of taking into consideration the immunity status of the population as one of the factors which determines age incidence of the disease.

Bottom page 13, paragraph beginning "let us now consider" continued on page 14. The data which have a bearing upon the influence of race can be compared only if it can be shown that the previous experience and circumstances of exposure (living conditions, etc.) are alike. Conclusion #7 is not established. The important point is not race. It is previous history and exposure. The American Army personnel were newcomers to the area in which they were exposed. In other words, the division would better be made on the basis of recent immigrant and native populations.

Page 14, tenth line from bottom: "there were thousands of others which were diagnosed as fever of unknown origin or dengue-
like fevers with pleocytosis, which were most probably non-paralytic poliomyelitis." How do you know?

Page 15. Enough work has been done in the laboratory already to indicate that there are immunologic differences in poliomyelitis strains. This is an experimentally determined fact. It must, therefore, be taken into account in attempting to explain any of the epidemiological manifestations of the disease. Furthermore, it must be kept in mind that an epidemic is, after all, an acceleration of a process which ordinarily goes on at an endemic level. The effect of an epidemic may be the equivalent of endemic prevalence spread over several years.

Page 15, second paragraph, paraphrasing your statement, it means that exposure to infection is more important as a factor than differences in racial resistance.

Page 16, Collins data: "If latent immunity is acquired at all, even though more slowly than among the poor, one would expect that there would be more of it at the age 10 to 14 than at the age 5 to 9, unless one assumes that the chances of picking up the infection is so much greater at 10 to 14 than at 5 to 9, that the acquired immunity is overshadowed." As in the preceding discussion, there are two variables. One is age-specific immunity status, and the other is the risk of exposure at different ages.

Page 17, Lansing antibodies. There is no evidence on which to base the assumption that Lansing antibody is a measure...
of exposure to the poliomyelitis virus which causes most of
the paralytic attacks in the areas from which these data have
been obtained.

Page 17, second paragraph: What is meant by "Poliomyelitis
is becoming less and less infantile"? In the United States,
the incidence of poliomyelitis, as measured by morbidity and
mortality in the age group under 5 years, is declining. There
is some indication that morbidity in the age group 5-9 has
shown a compensating increase (Gilliam-Dauer). There is as
yet no distinct indication that the incidence of the disease
is increasing at the older ages. It is by no means established
that the apparent increase in the older age groups may not be
accounted for largely, if not entirely, by better recognition
and reporting of the disease in this age group.