APPENDIX B

Discussion of Papers on Poliomyelitis by William H. Park, M.D., and Maurice Brodie, M.D., and by John A. Kolmer, M.D. October 1935

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Attempts to protect monkeys against poliomyelitis by means of inactivated virus did not arise with Dr. Brodie. Many investigators before his time made such attempts, and the results were so discouraging that the matter was dropped without pursuing it in man.

The favorable results reported by Dr. Brodie to have been obtained in monkeys admittedly depend upon his ability to titrate accurately and regularly 1 minimum completely paralyzing dose of virus. If this cannot be done, then all of his reported findings are invalid. Insofar as I know, no one has been able to obtain similar titration results, and this is not due to a lack of honest attempts on the part of other workers to do so.

At the beginning of this particular phase of his work, Dr. Brodie used in monkeys 1 or 2 doses of virus treated with 0.1 percent formalin for 12 to 16 hours at 37°C., and, according to him, favorable results were obtained. It is interesting to note that he said that just as good results were obtained with one dose of 5.0 cc. as with 2 doses of 5.0 cc. each. This does not sound reasonable unless both methods of application were without value. Indeed, that may be the case, because Dr. Schultz of California and Dr. Olitsky of New York have been able to show little, if, any, protection in monkeys vaccinated according to Dr. Brodie's method.

Recently, Dr. Brodie has been inclined to agree with others who hold that the complete inactivation of poliomyelitis virus spoils its antigenic qualities, and has been dispensing as vaccines, virus treated for 8 hours and 3 to 5 hours, respectively. He contends that the virus treated for this short

period of time is safe. However, he should be very careful not to decrease the time of inactivation further. If he does, he may run into an element of danger that one should attempt to avoid. Incidentally, Dr. Brodie now says that 2 doses are superior to one.

In vaccinating children, Dr. Brodie has wisely chosen a group of unvaccinated individuals as controls. After talking over the matter with him recently, I came to the conclusion that no case of poliomyelitis can as yet be ascribed to the use of his vaccine. Nor could I find any evidence for or against the efficacy of his vaccine. If you ask me for a prophecy, all I can say is: Provided Dr. Brodie does not make the time of inactivation of the virus too short, and provided he continues to administer the vaccine in the manner now employed, it will be reasonably safe but ineffective, particularly if one expects an appreciable degree of protection to persist for any great length of time.

It has been gratifying to see that Dr. Brodie and Dr. Park in approaching this problem have used the avenue of safety, although I do not believe that the vaccine will prove to be of any value as now used. I hope that Dr. Brodie and Dr. Park will continue their work until at least 100,000 children are safely vaccinated and that the results of all this work will be carefully brought together, so that we can get, once and for all, an absolute answer as to whether vaccine made in this manner and given in this manner is effective. If it is not, I hope that they progress still along the avenue of safety and arrive some day at an effective vaccine.

Attempts to protect monkeys against poliomyelitis by means of subcutaneous or intracutaneous inoculations of vaccines containing active virus did not originate with Dr. Kolmer. Many workers have made similar attempts and have found that, if sufficient amounts of such vaccines were given, protection could be produced in monkeys. On the other hand, these same workers also noticed that sooner or later an occasional monkey developed poliomyelitis as the result of the vaccination, and, for this reason, they considered it inadvisable to use such materials for the vaccination of human beings.

Dr. Kolmer has repeatedly stated that he has in his ricinoleated poliomyelitis virus a safe, efficient vaccine. On what grounds does he make such statements?

First, let us consider the matter of safety. In the issue of the *Journal of the American Medical Association* that appeared October 5, 1935, he says: "The safety of the vaccine is largely due to the fact that it is prepared from remote monkey passage virus that has apparently lost infectivity for human beings, just as the smallpox virus is changed by passage through the lower animals." He also states: "Attenuation of the virus with sodium ricinoleate may be an additional factor of safety, but the degree of attenuation is slight and of minor importance." In other words, Dr. Kolmer is

basing his claims for safety upon the fact that remote monkey passage virus is being used in the vaccine. A statement that monkey passage poliomyelitis virus is attenuated for man is nothing more than an assumption without experimental evidence to substantiate it. Investigators who are familiar with work in the virus field would not put too much dependence on such an assumption. For instance, yellow fever virus adapted to monkeys has caused the death of several workers. Furthermore, a number of virus diseases of lower animals are highly infectious for man, for example, psittacosis, Rift Valley fever, and louping-ill.

In this connection, Dr. Flexner has permitted me to say that poliomyelitis virus contained in the cord of human beings, when injected into the skin of monkeys, will paralyze an occasional animal. That is, a humanized virus without a single passage in animals can paralyze monkeys when given in the skin. Therefore, without definite proof to the contrary, one is not permitted to assume that a strain of poliomyelitis virus adapted to monkeys will not cause paralysis in human beings.

Dr. Kolmer admits that at least 10 cases of paralysis have occurred after 1 or 2 doses of his vaccine. He assumes that they were not caused by his vaccine but by a natural infection acquired through exposure. Pertinent information, however, regarding the time of onset of paralysis, the location of the first signs of paralysis and the mortality rate of such cases makes it essential that Dr. Kolmer definitely show that his vaccine is safe.

Now as to whether Dr. Kolmer's vaccine will actually protect human beings against poliomyelitis. In monkeys, he uses a certain amount of virus, administered in 5 doses, for each kilogram of body weight. Dr. Schultz and Dr. Olitsky have repeated Dr. Kolmer's work and failed to find as much immunity in their monkeys as was reported for Dr. Kolmer's. In children, Dr. Kolmer employs less virus per kilogram of body weight than was used for monkeys and it is administered in 3 instead of 5 doses. Such a procedure leaves us absolutely flat when we seek to make comparisons. Furthermore, Dr. Kolmer, as far as I can tell, unfortunately, has no comparable number of unvaccinated children, chosen in regard to age and location, to act as controls for the efficacy of the vaccine in the children receiving it. Thus it seems that we are to be left with a lack of definite knowledge regarding the value of Dr. Kolmer's vaccine as well as with a sense of uneasiness regarding its safety.

APPENDIX C

Conclusions and Recommendations of Nomenclature and Classification of Poliovirus, First International Poliomyelitis Conference, New York, July 14, 1948

I. *Poliomyelitis Virus.* This term should be used to designate the agent originally described as the cause of poliomyelitis. It is identified most readily by the character and distribution of its histological lesions in the spinal cord and by the characteristic pattern of the distribution of lesions in the brain.

A. *Substrains and Subgroups of Poliomyelitis Virus* have been identified by immunological methods. They are as yet poorly defined, with the exception of the Lansing-like group. Strains in this group have special properties of infecting cotton rats and mice (as well as primates). Normal human sera contain antibodies to this strain, and this and other reasons favor its inclusion as an example of true poliomyelitis virus.

II. Certain encephalomyelitis viruses which occur spontaneously in the mouse, such as Theiler's TO, FA, and GD VII, have been termed "mouse poliomyelitis" by some. It is proposed that this term be eliminated and Theiler's original designation of spontaneous mouse encephalomyelitis be used to describe these viruses.

III. It is proposed that the term "poliomyelitis-like" be eliminated from virological nomenclature.