March 17, 1954

Dr. H. A. Sissons
Department of Pathology
The Institute of Orthopaedics
Royal National Orthopaedic Hospital
234, Great Portland Street
London, W. 1, England

Dear Dr. Sissons:

I owe you an apology with regard to your letter of 16th December, 1953. Since it was addressed to my home and arrived at Christmastime it somehow or other became lost in a mountain of Christmas cards and greetings and was only recently discovered as part of a belated house-cleaning in preparation for the Easter season.

I also deeply regret that the work of several years with 8-aminoquinoline compounds has seen no more of the light of day than was contained in the few sentences in the abstract which you read in the American Journal of Diseases of Children. The reason for this is that after 3 years of arduous work I gave up this approach as unpromising and became interested in other problems. Now, with regard to your questions I might say the following: the compounds with which we worked consisted not only of those of the 8-aminoquinolines which were synthesized for malaria studies but also certain other compounds which were tailor made by our collaborating organic chemists. The animals used were rhesus monkeys, cynomolgus monkeys, and mice. The most striking effects were obtained after oral administration in rhesus monkeys of the compound known as plasmocid. This compound produced neuronal necrosis and degeneration in certain portions of the midbrain and medulla and, to a lesser extent, in the spinal cord, all of which are also very frequently attacked by the poliomyelitis virus; for example, the ocular motor nuclei, the vestibular nuclei, and a small proportion of anterior horn cells. This compound acted as a synergist with the poliomyelitis virus in the sense that it made the experimental infection worse. An isomer of this compound, called isoplasmodic, had no destructive action on the neurones although in very large doses it produced some reversible degenerative changes. This compound had a distinct retarding action on poliomyelitis and even prevented the disease in a significant proportion of rhesus monkeys inoculated by the intracerebral route. On the other hand, in cynomolgus monkeys which received the virus by mouth this compound had no significant effect on the incidence or severity of paralysis. A considerable number of other compounds were studied in this series with interesting variations in their effects on neurones but nothing that was ultimately worthwhile from the point of view of poliomyelitis emerged from that work.
I know that this probably does not help you very much but I hope it will give you a slightly better idea of what we were doing. You may or may not have seen two papers dealing with neurotoxicity of the 8-aminoquinolines by Ida G. Schmidt and L. H. Schmidt. They both appeared in the *Journal of Neuropathology and Experimental Neurology*: the first, 1949, Volume 7, page 368; and the second, 1951, Volume 10, page 231. Dr. L. H. Schmidt was one of the collaborators along with a number of organic chemists in the work that we had done.

With my humblest apologies and best wishes,

Sincerely yours,

Albert B. Sabin, M.D.

ABS/jcs

P.S.:

I am enclosing copies of two of the lantern slides which were shown at the meeting of the American Pediatric Society when the work was reported. These charts will give you a somewhat better idea of the nature of the compounds and the effect obtained in experimental poliomyelitis. You may keep the charts if you like.

The neuronal effect which was perhaps of the greatest interest to me was that produced by the compound methyl plasmocid. This compound is plasmocid (formula on the chart) with a methyl group in the 4 position on the quinoline ring. After oral administration of this compound all monkeys developed ptosis which lasted for several days and then slowly disappeared, even when the compound continued to be administered. Some of the monkeys sacrificed during the stage of ptosis revealed that the degenerative neuronal lesion was limited to the top portion of the oculomotor nuclei containing the neurones which are supposed to supply the levator palpebrarum.