APPENDIX E

Criteria for Live-Virus Vaccine Trials. World Health Organization Expert Committee on Poliomyelitis. Second Report. WHO Technical Report Series 145. Geneva, 1958

It has appeared to the Committee that studies on the use of attenuated strains of poliovirus as immunizing agents against poliomyelitis have reached a stage in which trials in man on a larger scale than has been attempted hereto are now indicated. This decision is based on the fact that preliminary tests on attenuated polioviruses in the hands of several investigators have failed to reveal signs of illness or other harmful effects in the vaccinees or their associates. It is the carefully considered opinion of the Committee, therefore, that the information which is now badly needed can only be obtained from field trials carried out on a larger scale than has been possible in the past. The Committee strongly recommends that such trials be carried out in the near future within certain specified population groups and areas and under the most careful supervision. In making this recommendation it is *not* the intention of the Committee that the use of attenuated strains should displace the use of an inactivated-virus vaccine in any of the areas where the latter is currently being used or will be used shortly, but rather that it should supplement it or substitute for it in areas where the use of the inactivated-virus vaccine is not feasible.

The special situations which the Committee believes will lend themselves best for this type of trial are: (1) in the face of an impending epidemic or at the periphery of an already existing epidemic; (2) where poliomyelitis of the infantile type is endemic and in particular within those areas where signs are indicative of an imminent shift to the epidemic form of the disease (see section 2.3.1, page 12); (3) to reinforce the immunity previously produced by an inactivated-virus vaccine. The value here would be that of the enhancement of the humoral antibodies as well as induction of resistance within the alimentary tract.

In temperate zones the trials mentioned under (2) and (3) should be carried out during seasons of the year when there is minimal spontaneous dissemination of naturally occurring poliovirus.

Criteria which should be fulfilled in the design of carefully controlled field trials which the committee has in mind are as follows:

(1) Such trials should be under the supervision of an individual who is experienced in investigations involving polioviruses, who has adequate laboratory facilities, to whom the assistance and facilities of consulting virologists may be available and who can devote an appreciable amount of time and direction to the project.

(2) The strains which are recommended for use in these trials should be selected with great care; this should be a most important part of the programme. At the present, those strains should be used which have been purified by the plaque method and which have already been fed to various small groups of adults and children and whose behaviour under these circumstances is well documented and appears to be satisfactory. A more detailed list of criteria is as follows:

(a) Progeny of triply purified plaques.

(b) Complete lack of paralytogenic activity on intracerebral inoculation of maximal doses (in excess of 10^7 TCD_{50}) in rhesus or cynomolgous monkeys and only minimal residual neurotropism by spinal inoculation in monkeys—i.e., only rare development of localized, nonprogressive paralysis in monkeys receiving doses of 10^6 TCD_{50} or more, and no "zone phenomenon" in which monkeys inoculated with smaller doses of virus develop paralysis more frequently than those inoculated with larger doses.

(c) Adequate and regular multiplication in the alimentary tract of nonimmune human beings should have been demonstrated with doses in the range of 10^5 TCD_{50} or less and these infections should be accompanied by an antibody response. Viremia should be either absent or rare and if virus is present it should be in minimal concentration.

(d) The strains used should have been tested extensively for any increase in the neurotropism of the virus excreted in the stools of human beings after varying periods of multiplication in the alimentary tract. The virus excreted in the stools and that derived from it in the first tissue culture passage should still exhibit distinct evidence of attenuation as determined by intracerebral inoculation of monkeys.

(e) The lots of virus to be used should be large enough to permit test feedings of at least one million individuals and these lots should have been produced under conditions comparable to those that might ultimately be used in the manufacture of still larger quantities. Each lot

should not only fulfill the requirements for neurotropic activity mentioned above (tested in at least 25 monkeys) but should also have been shown to be free of other viruses and bacteria as indicated by tests in tissue cultures, animals and bacterial culture media.

(f) Absence of harmful reactions in small groups of human beings should be demonstrated before a lot is used in increasingly larger numbers.

(3) It is suggested that the properties of these attenuated strains, which can be tested in the laboratory, be measured in a number of different laboratories so that there can be more than one opinion as to their pathogenicity or the lack of it.

(4) It is recommended that in all such trials the administration of the agents be done on a voluntary basis. It is also essential that such trials have the approval of local health authorities.

In conclusion it should be again stressed that the object of these trials and the need for carrying them out are based upon the belief that they may further reduce the prevalence of poliomyelitis.

Should these live-attenuated-poliovirus trials be successful, not only do they carry with them the hope that a more solid immunity against poliomyelitis might be achieved, but the possibility of eliminating or reducing the movement of virulent polioviruses within a given community might be realized—a result which the inactivated virus vaccine does not achieve.

APPENDIX F

Glossary of Terms

adenoviruses A large group (about 30 immunological types) of DNA-containing viruses first isolated by Wallace Rowe et al. (NIH) in 1953 from human adenoids (hence the name). Some types are known to cause epidemic respiratory diseases particularly among army recruits and in school-children. Several types are capable of producing cancer in hamsters.

adjuvant A material given together with a drug or vaccine to enhance its action. Some adjuvants form a depot of drug or vaccine at the site of injection, allowing a slow absorption of the material into the circulation and leading to a prolongation of the drug action or heightened immunological reaction.

agglutination Clumping phenomenon. The clumping of red blood cells and bacteria in the presence of specific antibodies to the cell or bacterium was a phenomenon early noted by immunologists. Many tests have since been devised to detect agglutination reaction (e.g., the tests used to detect the compatibility of donor and recipient in blood transfusing).

allergic encephalomyelitis A diffuse inflammation of the brain and spinal cord, resulting from an immunological reaction against the tissues of the central nervous system. In experimental animals, the condition can be produced by injecting them with homologous nervous tissue plus adjuvant. The condition simulates the postvaccination encephalitis seen in some cases following antirabies immunization (Pasteur treatment).

anaphylaxis A generalized shocklike condition ("anaphylactic shock") that may follow repeated contact with certain antigens. In 1913 Dr. Charles Richet received a Nobel prize for his contributions to an understanding of this phenomenon. It was also early described by Theobald Smith who found that some guinea pigs injected for a second time with horse serum or mixtures containing such serum collapsed and died in a minute or two with symptoms resembling those of an acute asthmatic attack. The discovery and understanding of the anaphylaxis process was one of the first indications that an immunological reaction is not always beneficial but can be harmful to the host as well.

aneurysm A localized dilatation of the wall of an artery due to a weakening of the vessel wall by a disease process (e.g., atherosclerosis) or by an infection (syphilitic aneurysm of the ascending aorta was once a common finding), or may be of traumatic or congenital origin (e.g., rupture of berry aneurysm of a cerebral artery is a prevalent cause of brain hemorrhage).

antibody A protein substance in the blood that defends the body against invasion by a foreign substance (antigen) by combining with the foreign substance and neutralizing it. Antibodies may be formed against such "foreign" substances as bacteria, viruses, and other infectious agents; or pollens, foods, drugs, red blood cells in transfused blood; or transplants of skin or organs from another person, etc. Antibodies are globulins and most are gamma globulins. That is