RESTRICTED

PRELIMINARY REPORT (No. 1)

on the

Vaccination of Man

against

Equine Encephalomyelitis (Western type)

by

The Neurotropic Virus Disease

Commission

of the

U. S. Army and other Board for the Investigation of and Control of Influenza

Epidemic Disease in the Army

Submitted August 1st, 1942

At the meeting of the Commission on December 3rd, 1941, the request was made by Colonel J. S. Simmons and Dr. F. G. Blake that evidence be weighed pro and con, with regard to the vaccination of troops against (epidemic) encephalitis. Information on the following points was desired:-

I. Evidence (serological or otherwise) of the protective value of such vaccines.

II. Possible dangers in the use of such vaccines.

III. Circumstances under which they might be used.

IV. Directions for their administration.

Inasmuch as most of the (epidemic) encephalitides are summer diseases, the Commission is submitting ~~the~~ a report (in preliminary form) at this time. It is only concerned with equine encephalomyelitis of the Western type (E.E.W.) and is largely concerned with one vaccine, viz. Lederle's formalinized (chick embryo) vaccine. We are not prepared to discuss equine encephalomyelitis of the Eastern type (E.E.E.), St. Louis or Japanese B encephalitis, or other encephalitic viruses on which members of the Commission are working.

It is obvious that the best means of answering major questions which have been posed would be to vaccinate large numbers (many thousands) of human volunteers with a variety of different vaccines and then to expose them to the disease so that one might compare the attack rate in the vaccinated groups with that of control groups in the same area. The opportunity

for performing such an experiment is not yet available and, as a substitute approach, we have chosen to observe the serological evidences of immunity which result in humans from vaccination against E.E.W. and to attempt to estimate what these serological evidences of immunity mean.

I. Specific points bearing on this question are:-

(a) Do persons given Lederle's Western encephalomyelitic vaccine develop antibodies?

(b) How soon do these antibodies appear?

(c) What response may be obtained with a single dose of the commercially available vaccine?

(d) Does the development of antibodies indicate that the vaccinated persons have become immune?

(a) The first question has already been studied at Duke University (1) where Beard et al., have reported on the speed at which neutralizing antibodies develop in humans vaccinated against both E.E.W. and E.E.E. and the duration of such antibodies, as well as the findings after a second vaccination.

Response to their vaccines as measured by serum-neutralizing antibody-content, was moderate (viz. between 100 and 10,000 mouse-infectious units - as determined by the intra-abdominal method) and more rapid for E.E.W. than E.E.E.

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(1) Beard, J.W., et al., J. Immunol. 38: 117, 1940, and ibid. 40: 497, 1941.

The duration of these antibodies was maintained for E.E.W. at a fair level for at least 6-9 months. Revaccination at this time resulted in the induction of neutralizing antibodies at levels 10 to 100 times higher than that noted with the initial course of vaccine.

Two more recent studies by the Commission (viz. by A. B. Sabin and his assistants, at the Children's Hospital Research Foundation, Cincinnati, and by L. T. Webster and J. Casals, at the Rockefeller Institute) have given more information, as follows:-

Experiment 1. Dec. 1941 - April 1942. Six volunteers were chosen from New Haven, Conn., (where presumably no cases of E.E.W. have ever been reported). Each was injected with 2 doses (1 cc. one week apart) of Lederle's (E.E.W.) vaccine Lot 10K3A (2). From each vaccinee a prevaccination and two post-vaccination specimens of blood were obtained. Tests on these specimens, (made by Webster and Casals) for both neutralizing and complement-fixing antibodies indicated that all individuals were negative prior to vaccination and that all developed neutralizing antibodies 18 to 21 days following vaccination, but failed to develop complement-fixing antibodies. (3).

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(2) The Commission is indebted to the Lederle Co. for this supply of vaccine.

(3) A tabular report of these results was included in the Report of the Neurotropic Virus Commission made on May 15th, 1942.

Experiment 2. April 1942-July 1942. Vaccination in Manitoba, Canada. The Province of Manitoba experienced a severe epidemic of Western equine encephalitis during the summer of 1941, and in the fall of that year the decision was made by Dr. F. W. Jackson (Deputy Minister of Health) to vaccinate a group of (adult, males) farmers within the 1941 epidemic area. (See Appendix, Section A.) These vaccinations were performed (on a voluntary basis) again using Lederle's vaccine (Lots 147H-2A, -4B, -5A, -6A, -8A and -9A) in May, 1942, and blood samples from 40 of the vaccinees were collected and sent by the Canadian authorities (4) to Dr. Sabin for neutralization tests. Dr. Sabin forwarded part of each specimen in the frozen state to Drs. Webster and Casals for the purpose of duplicate tests.

Dr. Sabin found that before vaccination 22.5 per cent of the 40 persons had neutralizing antibodies against ~~the~~ Western equine encephalomyelitis virus, while none of the 39 sera tested had neutralizing antibodies against the virus of St. Louis Encephalitis. One week after administration of one dose of 1 c.c. of the vaccine, only 17 per cent of 30 persons who were originally without antibody became positive, but with one exception the neutralization indexes were low. At the end

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(4) The Commission is indebted to the Hon. James McLenaghen, Minister of Health, to Dr. F. W. Jackson, Deputy Minister of Health and to Dr. C. R. Donovan, Director, Division of Disease Prevention - Department Health and Public Welfare, Province of Manitoba, Canada for their generosity and efficient cooperation in allowing us to study their material and in collecting it and sending it to Dr. Sabin.

of two weeks 46 per cent of the 13 people who received only the one dose of vaccine had neutralizing antibodies but only of moderate titre. On the other hand, all of 17 people who received an additional dose (1 c.c.) of the vaccine had neutralizing antibodies at the end of 2 weeks, and with but one or two exceptions the titres were very high.

Dr. Sabin concludes that the Lederle vaccine is adequate for the production of a high titre of neutralizing antibodies in two weeks when two 1 c.c. doses of the vaccine are used. Although no data were obtained to indicate what 2 c.c. or more as a single dose might have done, this vaccine does not fulfill all of the desiderata of producing neutralizing antibodies of moderate titre with one dose in one week. (See Appendix, Section B for details of neutralization experiments.)

Duplicate tests by Webster and Casals indicated close agreement with Sabin's neutralization tests and also that 2.5 per cent had complement-fixing antibodies in low titre prior to vaccination but that only an additional 5 per cent following vaccination.

From these two experiments it is concluded that persons inoculated with two doses of the Lederle Western equine encephalomyelitis vaccine generally develop neutralizing antibodies of high titre but no complement-fixing antibodies.

Evidence bearing on the last question (d), viz. whether the development of antibodies indicates that the vaccinated persons have become immune to the disease, has been sought from experiments on animals. Considerable data have already been collected on this point by Olitsky and his colleagues. (5) Although the species of choice for new experiments would probably be one which is naturally susceptible to the disease, such as the horse, mice were selected because of their availability in large numbers and the intracerebral route of infection was the first studied because of its uniformity of response. A series of such experiments have recently been performed by Drs. Webster and Casals. They are recorded in the Appendix, Section C. In brief these tests consisted in the vaccination of mice with both live and formalinized vaccine and subsequently testing the resistance of these mice to intracerebral inoculation and comparing this resistance with the titre of antibodies (both neutralizing and complement-fixing) found in the blood of the vaccinated animals at stated times.

On the basis of these "severe" tests, Webster and Casals have suggested that the titre of complement-fixing antibodies may parallel the degree of developing immunity

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(5) Morgan, I.M. and Olitsky, P.K., J. Immunol., 42: 445,1941; Morgan, I.M., J. Exp. Med., 74: 115, 1941 and Schlesinger, R.W., Morgan, I.M., and Olitsky, P.K., J.A.M.A. 119: 618, 1942.

more closely than do neutralizing antibodies. It should be mentioned, however, that there are no experiments reported on resistance developed to peripheral inoculation of virus, which may perhaps simulate more closely the "natural mode of infection". It is possible that a minimal amount of circulating antibody is associated with peripheral resistance but only a high degree of immunity is associated with cerebral resistance.

II. Dangers of, and reaction to, the Vaccination. Inasmuch as the vaccine used on humans in this series of observations was formalinized (and not live) virus, the dangers of inducing an experimental infection are not great.

In the studies by Beard et al., (1) it was reported that general aand local reactions to the initial course of vaccine (2 doses 2 c.c. each) were mild or absent (incidence not mentioned) except in one instance (1%) in which muscular stiffness of at least 4 months duration developed subsequent to vaccination. Reaction to the second course of vaccine (single dose 2 c.c.) were reported by the Beards to be "definitely greater than that to the first". This consisted in "malaise, slight mausea and weakness. In several instances cramping stiffness and indefinite muscular soreness in the lower thigh on the side of injection were felt, which persisted in 1 case (out of 9 in the series) several weeks, diminishing gradually and entirely disappearing finally. Local reactions at the site of injection were not seen."

The Manitoba vaccination experiment has now given us a much larger group of people vaccinated (for the first time) and the report to date (6) on these is that of approximately 3,000 people given the vaccine, about 1600 reports are now available. Of these approximately 114 persons (7%) were reported to have had both local and general reaction following the first dose and about 288 (12%) had both local and general reaction following the second dose. None of these reactions were serious insofar as could be ascertained and no one required treatment by a physician.

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(6) Dr. C. R. Donovan has kindly reported the findings to me as of the date of July 23, 1942.

III. Circumstances under which the vaccine might be used.

In spite of limited knowledge, vaccination would still seem to be a preventive measure worth trying under certain circumstances ~~and~~, as stated in the Commission's report of May 15th, 1942, ~~the indications for the use of Lederle's formalinized chick embryo vaccine may be:~~

Vaccination is only one of several measures which may be put into effect as possible control measures in this disease. Chief stress should be placed on Sanitary Corp activities, which should exert all preventive measures possible whenever cases of critically diagnosed E.E.W. are occurring in the civilian population in the neighborhood of Army establishments. When, and only when at least 2 or 3 definitely diagnosed cases have occurred should vaccination be contemplated and then offered on a purely voluntary basis.

More specifically, the vaccine can be used when E.E.W. which has been diagnosed with reasonable accuracy appears in a given area in epidemic form. This would be regardless as to whether other types of encephalitis may be suspected or proven to be present within the same epidemic area at the same time. Under these circumstances, it would seem wise to regard all troops within such an epidemic area as possible candidates for vaccination — but particularly troops on manoeuvres which are apt to have more exposure to mosquitoes than other groups.*

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*No specific reports are as yet available as to the reactions to this vaccine in men who are on active duty and undergoing a moderate amount of physical strain, but to all intents and purposes this was the case with a fair percentage of the farmers vaccinated in Manitoba in May, 1942.

Inasmuch as the amount of vaccine at present available (for purchase) is not large (and the time required for its production of new vaccine is about 40 days) no large-scale vaccination program can be planned by the Army this summer, but it is proposed that if and when it is necessary to keep troops within certain epidemic areas or to move troops into such epidemic areas, we believe that the vaccine should be administered on a voluntary basis to as large a group as is practical. We believe that under such circumstances, if the number of men volunteering to be vaccinated should be over 50, that the Commission should be notified and that one or more of its members should assist in the "experiment". Every effort could then be made to follow the vaccinated group and to compare their disease record with that of unvaccinated controls.

IV. Directions for Administration of Vaccine. There are no indications that the technique of administering Lederle's chick embryo vaccine (E.E.W.) should be altered from those used in the Canadian experiment, viz. that 2 doses be employed, 1 c.c. each, and that they be given one week apart.

Respectfully submitted,

John R. Paul
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Neurotropic Virus Diseases.