477 First Avenue  
New York 16, N. Y.

Memorandum to: Dr. Stokes  
Dr. Gauld  
Dr. Smadel  
Dr. Paul  
Dr. Havens  
Dr. Sabin

Enclosed is a copy of the minutes of the special meeting of 27 June 1951 in New York on the subject of hepatitis and Japanese B encephalitis.

Sincerely yours,

Colin M. MacLeod, M. D.  
President, AFRB

EBW
Minutes of the Special Meeting. Armed Forces Epidemiological Board.
27 June 1951, New York

Subject: Hepatitis and Japanese B Encephalitis

Present: Dr. Stokes, Dr. Gauld, Dr. Paul, Dr. Havens, Dr. Hammon, Colonel McNinch, and Dr. MacLeod, Chairman

Hepatitis

Dr. Stokes was first asked to review the background and present status of the hepatitis gamma globulin program for Korea. He stated that the total supply of gamma globulin now available for this purpose is 2,000 liters put up in 2 cc. ampoules. The number of persons to be immunized is unknown, but this will be adequate. In the last two outbreaks studied, a dosage of .01 ml. per pound was found to be effective, and he proposes to use 2 cc. per man, since the average weight of a soldier is 150 pounds. There is some question as to whether the strain of hepatitis virus active in Korea is the same as those active in the outbreak studied in this country in which gamma globulin was effective. However, it seems probable that gamma globulin will be equally effective. The plan to be carried out in Korea is not designed primarily as an experiment, for it is considered that studies already carried out have indicated that gamma globulin in the dosage to be given is effective. This will be a prophylactic program rather than an experiment. It is planned to inject all replacements, beginning prior to the epidemic season for hepatitis, probably in September or October. Those troops already in the area will not be injected. They may serve to some degree as controls. Only one injection of gamma globulin will be given; the replacements will be inoculated as they arrive, continuing during the winter months. Time for discontinuing has not been determined. Dr. Stokes plans to be present in the area with a team to supervise the injections himself. It has not been determined whether the injections should be performed in Korea or in Japan before troops are moved into Korea.

The following recommendations were made as a motion, seconded and passed:

(1) To inject each replacement with 2 cc. of gamma globulin beginning in September of 1951.
(2) This program of inoculation will be discontinued as of 1 March 1952.
(3) Data will be evaluated at the end of this study before any further recommendations will be made regarding continued use.

Dr. Hammon raised the question as to how best to answer Colonel Hullinghorst's question regarding the safety of gamma globulin from the standpoint of hepatitis. Dr. Stokes will write Colonel Hullinghorst a letter informing him that no case of homologous serum
hepatitis has ever been known to develop following injections of gamma globulin. Gamma globulin cannot be heated at the necessary temperature to inactive hepatitis virus as is done with human albumin. It is not considered that any such treatment is necessary for gamma globulin. Possibly during the fractionation and concentration procedures used in preparing gamma globulin, the virus is left in the albumin fraction or is destroyed during the processing of the gamma globulin.

Japanese B Encephalitis

Dr. Hammon was asked to review the background and progress to date regarding the projected studies on gamma globulin for passive protection against Japanese B encephalitis. He pointed out that vaccine had not proved to be the perfect immunizing agent since (1) it required almost 2 months to produce immunity, and during certain types of operation persons must enter an epidemic area without 2 months in which to prepare them by active immunization procedures; and (2) vaccine has failed to protect many persons against the clinical disease even though the standard immunization procedures have been carried out. For this reason it was felt wise to study the possibility of using gamma globulin prepared from an immune adult population such as the Japanese in the Tokyo-Yokohoma area. This passive immunizing procedure would be recommended for use only in epidemic areas at the time an epidemic is actually anticipated on the basis of observing beginning cases in a known endemic area. It would not necessarily replace vaccination if successful, but would supplement it. Correspondence has already been carried on between Col. Hullinghorst and the Ad hoc Japanese B Committee and certain progress has been made. It is planned to attempt to evaluate passive prophylaxis and the antibody content of gamma globulin in the laboratory before any field test is made. It would not be possible under any circumstances to undertake a field test before 1952.

Colonel Hullinghorst wrote on 13 June that the Takeda Pharmaceutical Industries, Ltd., an affiliate of Merck and other German companies, Ciba of France and American Cyanamid, the largest and probably the most dependable commercial producer of drugs in Japan, has an excellent biologics division and has been initiating a program for gamma globulin production for the Japanese market to be used for prophylaxis of measles and for Japanese encephalitis. He has been assured by the Public Health and Welfare officials that this company is well qualified and should be capable of producing a product acceptable for use. As a result of the conference which he has held with the representatives at Takeda they have agreed to attempt to have at least 100 cc. of finished product meeting F.S.A. specifications by 1 August. This will be purely for experimental purposes and will be forwarded to Dr. Hammon; Colonel Hullinghorst also expects to get an additional amount for his own investigations. He plans to inoculate a group of susceptible horses, then expose these
normally in an endemic area during the summer months to see whether the gamma globulin will prevent inapparent infection which might otherwise be expected to occur. The gamma globulin made by the Takeda Company will be prepared from human placentas.

It was agreed that Dr. Hammon should advise Colonel Hullinghorst to proceed with obtaining the experimental lot of placental gamma globulin. Also, the group felt that the experiment planned by Colonel Hullinghorst was well worthwhile.

Considerable time was then devoted to discussion of the laboratory tests which should be done here. Dr. Hammon indicated that he was preparing hyperimmune Japanese B mouse serum to be used in passive protection experiments with mice. These should be complete within a few months. When the gamma globulin has been received it was planned that it would be inculcated in human volunteers in varying dosages and the antibody level of the serum of those volunteers followed at intervals until the gamma globulin had disappeared. Dr. Hammon pointed out that he had no facilities for obtaining human volunteers. It was agreed that Dr. Stokes would approach Dr. Ains McGuiness to see if he would be willing to undertake the human volunteer work. The specimens of blood from those volunteers could be divided and run in Dr. Hammon’s laboratory and in another laboratory to be designated. It was believed that about 15 volunteers would be necessary and that they should be bled at least at weekly intervals for a period of 2 to 3 months. Antibody titrations should be run in parallel with the intracerebral and the intraperitoneal test in baby mice.

It was suggested that as a measure of the potency of Japanese gamma globulin it would be wise to have a few tests run against influenza, diphtheria toxin, and possibly mumps and Lansing poliomyelitis viruses. A very small amount of gamma globulin would be necessary for these tests. Dr. Havens agreed to run the diphtheria antitoxin tests; Dr. Stokes felt that Dr. Sigel would be willing to test the mumps; and Dr. Hammon indicated that in his laboratory (Dr. Cheever), or perhaps with the assistance of Dr. Salk, both influenza and Lansing could be run.

Next, it was suggested that since Col. Hullinghorst had indicated there was plasma available from outdated blood in the 406th’s Blood Bank, which receives both Japanese and American blood, he be requested to prepare a pool of Japanese plasma and a pool of plasma from Americans who had been on duty in Korea at the time of exposure there, sending half of this pool to United States for processing and having the Takeda Company process the other half. In this way it would be possible to determine how satisfactory a product could be prepared by the Takeda Company. Gamma globulin from both sources -- Japan and United States -- would be tested in Dr. Hammon’s laboratory for Japanese B antibody. The serum from the Americans from Korea would also be tested to explore the possibility of using such a source of antibody. If this plasma is obtained Dr. Havens will request Dr. John W. Palmer of E. R. Squibb to process the portion sent to this country. It was felt that 5 to 10 liters of plasma should be available as starting material for each of the lots sub-
mitted to any one person to process.

It was next agreed that before entering into any contract or making any definite arrangements with the Takeda firm for supplying large amounts of gamma globulin for field work in 1952 we should await the results of the tests on human volunteers to determine whether titers such as those obtained by vaccination are present at the end of 3 weeks in persons given a reasonably small dose of the Japanese gamma globulin. If exceedingly large quantities of gamma globulin are necessary to produce such antibody levels, no field trial should be planned. However, in the meanwhile, it is felt that Colonel Hullinghorst should continue to explore the possibilities of large-quantity production by the Takeda firm.

The problem of a consultant to visit the Takeda firm was next considered. It was decided that conversations should be initiated with Dr. Cohn's group at Harvard regarding finding the right person to go to Japan. Before such a consultant is approached, however, it was felt desirable to have information on the product currently being made by Takeda. He should be a person who knows the technical problem involved in processing gamma globulin.

Dr. Hammon was authorized to write Colonel Hullinghorst of the decisions made at this meeting.

Vaccination against Japanese B encephalitis. Dr. Paul summarized the efforts made to date to evaluate the effectiveness of Japanese B vaccine. Conclusions which had been made at other meetings, that the vaccine was of little or possibly no value, it was pointed out had been challenged by Dr. Sabin who feels that the diagnosis of the cases included in the studies was not on an adequately solid basis, and that he insisted that evaluation must be made only on proven cases. Colonel Hullinghorst has sent complete clinical summaries and laboratory data and vaccination status on 25 cases from Korea. These were first sent to Dr. Sabin and he has submitted to Dr. Paul his interpretations on these cases. His interpretations do not agree with those made by Taylor, Hullinghorst and Gaul. Dr. Sabin feels that suspicion should fall on the serological tests for Japanese B encephalitis now being performed at the 406th Laboratory. Dr. Sabin forwarded the data on the 25 cases to Dr. Hammon, and Dr. Hammon has prepared an analysis which he brought to the meeting. There was not time to make a comparison of the two as a group, but a quick glance by Dr. Hammon indicated that there was partial agreement between his analysis and that of Dr. Sabin but by no means a complete agreement either as to clinical diagnosis based on summaries or on interpretation of laboratory work. Dr. Hammon pointed out that it was impossible to interpret the complement fixation at this time since the statement occurred twice in the Annual Report of the 406th that the serum dilutions were final serum dilutions. Yet in another section dealing with an experiment with horses it was stated that the serum dilutions were original serum dilutions. Formerly, at the 406th Dr. Hammon knew that original serum dilutions had always been reported. If serum dilutions of 1:4 and 1:8 were the highest obtained with many patients and these
actually represented undiluted serum and serum diluted 1:2 by the normal method of reporting, he felt that the tests were of no value whatsoever and had no significance. It was also pointed out that a number of cases which had been diagnosed clinically and had neutralizing antibodies failed to develop any complement-fixing antibody within a reasonable period of time. Experience by Sabin and Hammon and Tigertt on Okinawa and in Japan and Guam over a period of a number of years indicated that complement-fixing antibodies of at least a level of 1:4 or 1:8 (original serum dilution) should be present in almost 100% of confirmed cases. Up until the recent Korean outbreak mild cases of Japanese B encephalitis resembling nonparalytic poliomyelitis had not been confirmed by any laboratory diagnostic method. However, a rather large percentage of those in Korea were diagnosed as Japanese B encephalitis but were cases of a relatively mild nature. It was agreed that more information was necessary in regard to how the complement fixation test was now performed at the 406th Laboratory and that it would be wise to have a group of possibly 25 sera sent to the Army Medical School for checking. Part of these might be sent to Dr. Hammon's laboratory for additional testing. Dr. Hammon suggested that some of the antigen might also be sent to this country for test. The question of final or original serum dilution must be clarified.

It was pointed out by Dr. Paul that Dr. Snadel feels that the vaccine has little or no value as prepared and used at present and, therefore, vaccination should not be played up until we have a better vaccine available.

The question of adjuvants was next discussed and Dr. MacLeod felt that this should be investigated. It was pointed out that Dr. Sabin felt the same way but that Dr. Snadel opposed it since the vaccine contains such a high percentage of chick tissue. Dr. Hammon also felt that until the vaccine could be prepared with less protein material adjuvant studies might be delayed.

Dr. Paul stated that the Virus and Rickettsial Commission should advise the Army in the very near future regarding orders of vaccine for 1953 since it must be ordered about 18 months in advance. He felt that the advice should be on a scientific rather than on a political basis. The Army itself would have to decide whether it should be used even if it had not been demonstrated to have protective value.

The meeting was adjourned at 12:35 p.m.

W. McD. Hammon