

ANNUAL REPORT

to

The Commission on Viral Infections
of the
Armed Forces Epidemiological Board

For the Period: 1 March 1956 to 28 February 1957

Title of Project: Studies on Hepatitis

Responsible Investigator: Dr. Robert Ward, Professor,
Dept. of Pediatrics

Principal Professional Assistants: Dr. Saul Krugman
Dr. Joan P. Giles

Contract Number: DA-49-007-MD-477

Name of Institution: New York University College of Medicine

RG: 112
Accession # 64A-2161
Box # 134
File Name: Dr. Saul Krugman MD-477

Abstract of Report

Since 1953 over 350 cases of hepatitis with jaundice occurred among 4000 mental defectives at Willowbrook State School, Staten Island, N. Y. Epidemiological evidence suggested that the disease was probably infective hepatitis. The following questions were asked:

1. Would gamma globulin prevent its spread?
- 2 Can "passive-active" immunity be induced?

Results have shown:

1. Gamma globulin (0.01cc per lb.) apparently reduced the incidence of hepatitis in a group of 1200 inmates as compared with 3000 uninoculated controls; attack rates per 1000 during 30 weeks following gamma globulin were 7.5 and 18, respectively. This study is being repeated with an increased dose of gamma globulin (0.06 cc per lb.)

2. Attempts to induce "passive-active" immunity were begun: 10 subjects received gamma globulin followed by ingestion of active virus; 5 subjects received virus only. The source of virus was a fecal suspension prepared from jaundiced patients at Willowbrook. The suspension was made bacteria-free by centrifugation, heating at 56° C for 30 minutes, and antimicrobials. Inoculation of tissue cultures, suckling mice, and monkeys yielded no virus. Titration by mouth produced mild hepatitis with jaundice in 18 subjects. The incubation period ranged from 39 to 67 days. The 50 per cent infectivity end point was about 1 gm. of stool.

REPORT

Studies on hepatitis at the Willowbrook State School, Staten Island, N.Y. for mental defectives have yielded the following information:

1.) Titration of stool suspension: Feces collected in first week of jaundice from patients at Willowbrook were pooled in aqueous suspension and rendered free of bacteria by centrifugation, heating at 56°C and by antimicrobials. No viruses were detected by inoculating the suspension in various tissue cultures, suckling mice and monkeys. This material was titrated by mouth in human subjects between the ages of 3 and 10 years newly admitted to isolation quarters. The results are shown in Table I.

TABLE I
Titration of Willowbrook Stool Pool

Trial	Dilution of suspension 1 to	Volume ml.	gm. of stool	Result: Hepatitis with jaundice
3	5	20	4	*12/13
2	10	10	1	5/11
	(10	1	0.1	1/8
1	(1000	1	0.001	0/8
	(100,000	1	0.00001	0/8

* Numerator: number developing hepatitis with jaundice.
Denominator: number fed.

The titration was carried out in three separate trials beginning with the highest dilutions and working toward the lowest. None of the children became seriously ill. Most had a very mild transitory illness with slight

icterus and positive liver function tests. The incubation period was unusually long for infective hepatitis. It ranged from 39 to 67 days and was no shorter in those receiving 4 grams as compared with those given one or 0.1 gram of stool. This is the first reported titration of hepatitis virus in feces. A fair amount of this known positive material is available.

2.) "Passive-active" immunity. A) An attempt has been made to induce "passive-active" protection as follows: 15 children were admitted directly from their homes to an isolation ward at Willowbrook. Ten were infected with gamma globulin (G.G.), 0.06 cc per pound of body weight. About one hour later all 15 subjects were fed 10 cc of 20% stool suspension (2 gm. of stool). At this writing 50 days later, only 2 of 5 controls have developed hepatitis with jaundice and none of 10 receiving G.G. It is planned to test the immunity of this group by feeding homologous virus a few months hence.

B) At the end of June, 1956 approximately 1/3 of the Willowbrook population of each building was inoculated with G.G., 0.01 cc per lb. A total of 1224 patients received G.G. and 2988 were left as uninoculated controls. In addition, 125 employees volunteered for G.G. and received it, while 456 did not. The results are shown in Table 2 and Figure I.

Table 2

Gamma globulin and Hepatitis at Willowbrook. 1st Trial.

Population	No. of individuals	Hepatitis with Jaundice		
		No. of patients	rate per 1000	P
Inmates - gamma globulin*	1224	9	7.5	(.02-
Inmates - control	2988	55	18	(.01
Employees- gamma globulin*	125	4	32	
Employees- control	456	8	17	

* 0.01 cc per lb.

** Over a 7 month period following gamma globulin.

A total of 65 patients (or inmates) developed hepatitis with jaundice at some time during the observation period of 7 months. Nine of these had received gamma globulin, and 55 had not. The attack rates for the gamma globulin group and controls were, respectively, 7.5 and 18 per thousand. This appears to be significant at the 0.02 level.

The distribution of hepatitis with jaundice by week of onset of illness is shown in Fig. 1. Although cases of hepatitis continued to crop out in those who had received G.G., the attack rate was about one-half that of the controls. There were several stretches of 4 to 5 weeks during which no jaundice occurred in the G.G. group although cases appeared in the controls.

Among the attendants the opposite happened. Of 125 who got G.G. 4 cases occurred - an attack rate of 32 per 1000. Of 456 uninoculated controls, 8 cases occurred - or 17 per 1000. The reason for this is not clear, but the employee groups were relatively small and conditions of exposure were different from those of the patients.

C) On January 24-25, 1957, a second large-scale trial was begun with the purpose of testing a larger dose of G.G. The patients who had never received G.G. (approximately 3000) were divided in half. G.G. 0.06cc per lb. was given to half of this group in each building. The other half remained uninoculated. Since this is written on February 1, 1957, the results of this trial will be reported later.

FIG. 1.

