GAMMA GLOBULIN PROPHYLAXIS*

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THE importance of infectious hepatitis as a world-wide problem has been highlighted in detail during the presentations made at this symposium. It is clear that as of today (May 18, 1968) there is no published report confirming the isolation of infectious hepatitis virus in a tissue-culture system or animal host. Experience with poliomyelitis, measles, and rubella has revealed that the time interval between isolation of the virus and subsequent vaccine development and licensure has ranged between seven and nine years. Poliomyelitis vaccine was first licensed for use in 1956; the virus was isolated in 1949. Measles virus was identified in tissue culture in 1954; the vaccine was licensed in 1963, nine years later. Although rubella virus was isolated in 1962, it is unlikely that a vaccine will be licensed before 1969. Consequently, it seems logical to predict that a vaccine for the prevention of infectious hepatitis will not be developed and licensed before 1975.

FIVE GAMMA GLOBULIN TRIALS

This discussion of the use of gamma globulin in infectious hepatitis is particularly important because it is unlikely that an active immunizing agent will be available for the prevention of the disease during the next decade. The efficacy of gamma globulin for the prophylaxis or modification of infectious hepatitis has been well documented by many investigators during the past 23 years.[1-7] I should like to devote the limited time available to describing the results of five gamma globulin trials conducted in collaboration with Joan P. Giles at the Willowbrook State School, Staten Island, N.Y., an institution for mentally retarded children.** The endemic nature of the disease in this institution has been described in detail in previous reports.[4, 5]

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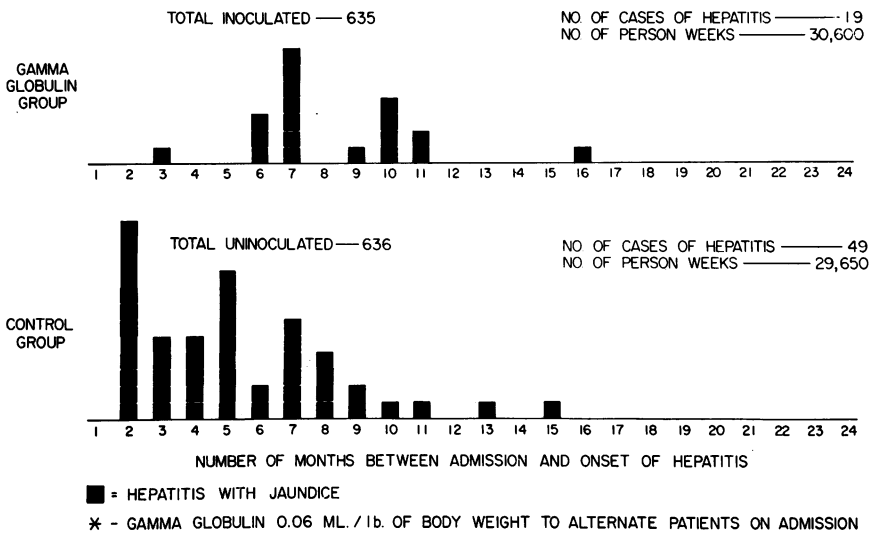

Fig. 1. Effect of gamma globulin on the incidence of hepatitis with jaundice in newly admitted patients at the Willowbrook State School (February 1, 1958 to February 1, 1960). Note the significant protective effect during the first five months after admission: 31 cases of hepatitis in the control group as compared with one case in the group given gamma globulin.

First trial. The first trial was begun on February 1, 1958. During the subsequent two-year period, 1,271 patients were admitted to the study. Alternate patients on admission to the institution received an inoculation of gamma globulin, 0.06 ml. per pound of body weight. As indicated in Figure 1, the gamma globulin group included 635 patients who were observed for 30,600 person weeks. The uninoculated control group of 636 patients was observed for 29,650 person weeks. The two groups were comparable in regard to age and type of exposure. Approximately 75 per cent of each group were children.

During the first five months there was a striking difference in the incidence of hepatitis with jaundice—31 cases in the control group and only 1 case in the gamma globulin group. During the subsequent period of observation (6 to 24 months), 18 cases of hepatitis were detected in each group.

The design of the first trial was such that only patients with frank jaundice were recognized; no attempt was made to detect anicteric cases. Under the conditions of this study gamma globulin, 0.06 ml. per pound of body weight, provided protection for at least five months

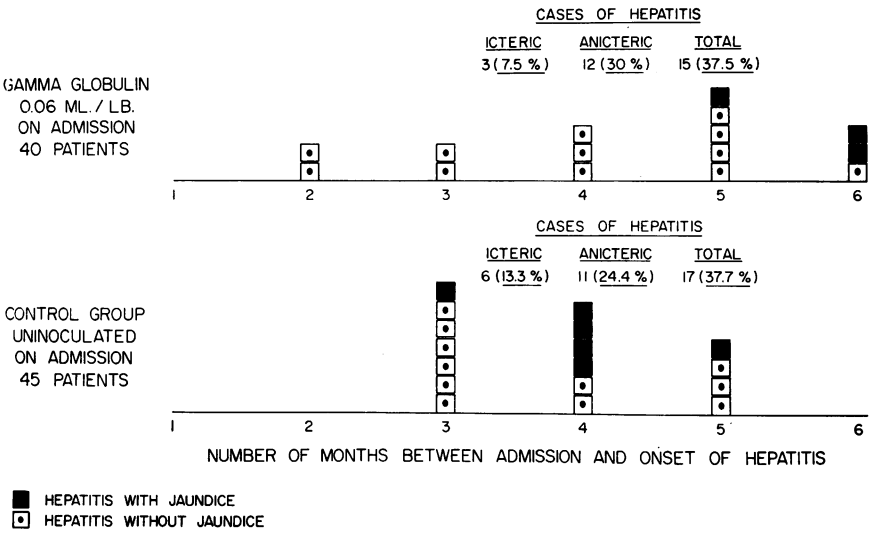

Fig. 2. Effect of gamma globulin on the incidence of infectious hepatitis with and without jaundice. Note the delay in appearance of jaundice until the fifth month and the decreased number of icteric cases in the group given gamma globulin.

after admission to the endemic area. The possibility that mild or inapparent infection might have occurred in some of the persons "protected" by gamma globulin was investigated in the second trial.

Second trial. Of 85 newly admitted patients, 40 received gamma globulin, 0.06 ml. per pound of body weight; the remaining 45 patients were uninoculated controls. Patients in both groups were observed during 1959 and 1960. All children were observed closely for 6 months, and liver function tests were performed at least once each week. Criteria for a diagnosis of anicteric hepatitis included a crescendolike rise in serum glutamic oxaloacetic transaminase (SGOT) activity plus abnormal thymol turbidity.

The results are shown in Figure 2. The over-all attack rate was the same for both groups. Six cases of jaundice occurred in the controls as compared with three in the gamma globulin group. Moreover, the jaundice appeared two months later in the gamma globulin group, at five months. Evidence of hepatitis was demonstrated in 12 of 40 patients in the gamma globulin group within five months of admission to the institution. This occurred despite a dose of gamma globulin which is considered not only adequate but large.

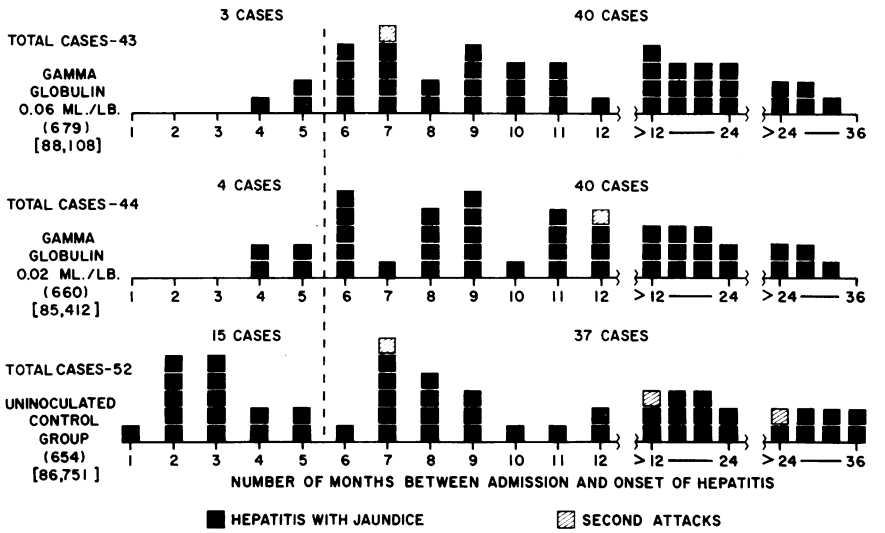

Fig. 3. Effect of various doses of gamma globulin on the incidence of hepatitis with jaundice in newly admitted patients at the Willowbrook State School (July 1, 1960 to September 1, 1964).

It is clear that under the conditions of this trial gamma globulin did not prevent hepatitis infection; it appeared to suppress jaundice and to modify the disease so as to make clinical recognition more difficult.

Third trial. The third trial was designed to study the effect of various doses of gamma globulin on the incidence of hepatitis with jaundice. This study was in progress during the period of July 1, 1960, to September 1, 1964. Newly admitted patients were assigned to one of three groups in rotation: 1) a gamma globulin group, 0.06 ml. per pound of body weight; 2) a gamma globulin group, 0.02 ml. per pound of body weight; and 3) an uninoculated control group.

The results of the third trial are shown in Figure 3. Comparison of the gamma globulin and control groups revealed significant protection against jaundice for the first four or five months after admission to the institution. The smaller dose (0.02 ml.) seemed to be as effective as the larger dose (0.06 ml.). A single inoculation of gamma globulin provided no protection after five months. Accordingly, a fourth trial was designed to determine the prophylactic effect of two doses of gamma globulin given at five-month intervals.

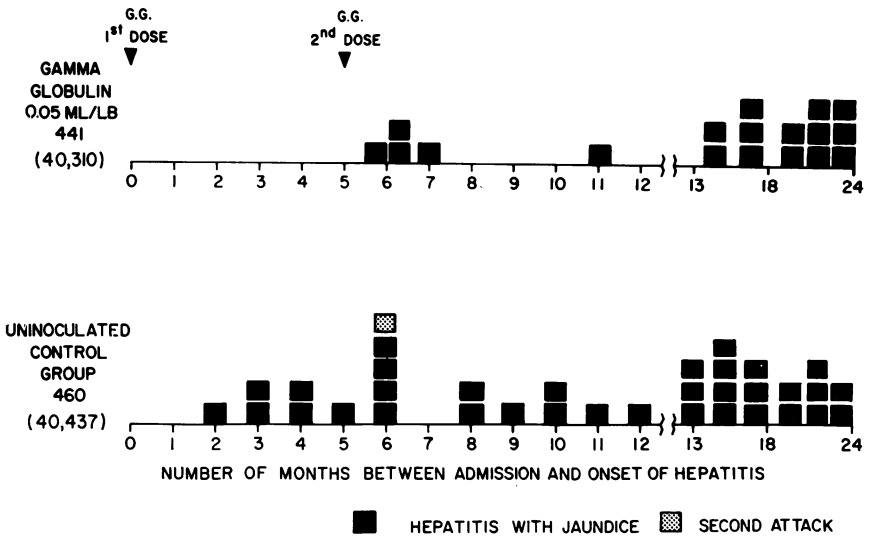

Fig. 4. Effect of two doses of gamma globulin on the incidence of infectious hepatitis with jaundice (November 1, 1963 to November 1, 1965).

Fourth trial. The fourth trial was in progress during the two-year period of November 1, 1963, to November 1, 1965. Alternate patients received two doses of gamma globulin, 0.05 ml. per pound of body weight, one inoculation on admission, and one five months later. The gamma globulin group included 441 patients who were observed for 40,310 person weeks. The uninoculated controls included 460 patients observed for 40,437 person weeks.

The results of the fourth trial are shown in Figure 4. During the first year 17 cases of hepatitis with jaundice were observed in the control group as compared with four in the gamma globulin group. Moreover, at least one and possibly two patients were in the incubation period of hepatitis when the second dose of gamma globulin was administered. After 12 months no significant difference was observed in the incidence of icteric hepatitis.

Under the conditions of this trial two doses of gamma globulin given at a five-month interval provided good protection against hepatitis with jaundice for at least one year. It is likely that this regimen would have a similar effect in any endemic area where persons may be subjected to a similar type of continuous and prolonged exposure. The

TABLE I. FIFTH TRIAL. EFFECT OF GAMMA GLOBULIN ON THE INCIDENCE OF HEPATITIS WITH JAUNDICE IN WILLOWBROOK PERSONNEL DURING FIRST YEAR OF EMPLOYMENT

Year	*Gronp*	*No. at risk*	*Hepatitis with jaundice*		
			No.	*Per cent*	*Reduction (per cent)*
1960 to 1962	No GG	190	11	5.8	80
	GG, 4 ml.	177	2	1.1	
1962 to 1965	GG, 4 ml.	1,560	8	0.5	80-85*

*Estimated reduction of 80 to 85 per cent is based on a 4.0 to 4.5 per cent annual attack rate of hepatitis with jaundice in newly admitted Willowbrook patients during the period 1960-1965.

type of exposure in Korea that has been described by Marcel E. Conrad was different. Hepatitis in the military personnel was most prevalent during the latter part of the first year. Consequently, if the first dose of gamma globulin were given at the time of departure from the United States, its effect would have waned before adequate exposure was encountered.

Fifth trial. The fifth trial represents an experience with employees at the Willowbrook State School. Since 1960 gamma globulin has been used for the protection of nurses, hospital attendants, kitchen, and laundry personnel employed at Willowbrook. From 1960 to 1962 the gamma globulin was offered to all new employees on an optional basis; it was accepted by 190 and refused by 177. Since 1962 it has been administered routinely to all new employees.

As indicated in Table I, a single dose of gamma globulin (16 per cent solution, 4 ml.), administered intramuscularly, approximately 0.03 ml. per pound of body weight, provided significant protection. The administration of gamma globulin was followed by an 80 to 85 per cent reduction in the incidence of hepatitis with jaundice.

OTHER GAMMA GLOBULIN STUDIES

The results of an interesting study in the Soviet Union were presented to the Expert Committee on Hepatitis of the World Health Organization in Geneva, December 10 to 16, 1963. E. A. Paktoris of the Ivanovski Institute of Virology, Moscow, U.S.S.R., described a controlled study which involved more than 100,000 school children in Estonian communities.[8] In two concurrent trials, gamma globulin was

TABLE II. RECOMMENDED DOSE OF GAMMA GLOBULIN FOR PROPHYLAXIS OF INFECTIOUS HEPATITIS

Type of exposure	*Dose ml./lb.*	*Total dose* ml.*
Single or short term	0.01-0.02	0.5 (up to 50 lb.) 1.0 (50 to 100 lb.) 2.0-3.0 (over 100 lb.)
Prolonged or continuous	0.03-0.06	1.0-2.0 (up to 50 lb.) 2.0-3.0 (50 to 100 lb.) 5.0 (over 100 lb.)

*Repeat once after five months if exposure is continuous.

administered: 1) to 50 per cent of the children in each class in all schools of one area; and 2) to all children in half the schools of another area. In the first trial the attack rate for an 11-month period was 17.9 per 10,000 in the gamma globulin group as compared with 45.3 per 10,000 in the control group. In the second trial the attack rate was 12.2 per 10,000 in the gamma globulin group as compared with 132 per 10,000 in the control group. The striking difference in the lower incidence of hepatitis in the controls during the first trial (45.3/10,000) as compared with the higher incidence in the controls during the second trial (132/10,000) may have been the results of decreased exposure because half the children in each class were protected by gamma globulin. These studies suggested that hepatitis modified by gamma globulin may be less contagious than the unmodified disease.

CONCLUSION

The results of the gamma globulin studies which have been described confirm the efficacy of gamma globulin for the prevention or modification of infectious hepatitis.

INDICATIONS FOR GAMMA GLOBULIN

Gamma globulin is recommended for children or adults who have had an exposure which is likely to result in infection. Since the disease is transmitted by the fecal-oral route, direct, close contact is required for an adequate exposure. If a person with hepatitis were a food handler the infection could be spread by indirect means through the ingestion of contamined food. Infectious hepatitis may also be transmitted by the parenteral route.

Persons living in the same household who are subjected to intimate direct or indirect contact with a case of hepatitis should receive gamma globulin. On the other hand, the routine administration of gamma globulin is not indicated for children and adults in schools, offices, and factories. In institutions for the mentally retarded and other closed facilities such as prisons, gamma globulin may be indicated for new admissions or new employees if hepatitis is endemic in these areas. Hospital personnel who care for infected patients will not require gamma globulin if appropriate hand-washing procedures are employed and if there is no obvious break in technique.

Dosage

The dose of gamma globulin is dependent upon the type of exposure: for example a single or brief contact (less than two months) or a more prolonged and continuous type (more than three months). The recommended dosage by milliliters per pound of body weight or by a more convenient total dosage schedule is shown in Table II.

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