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# VIRAL HEPATITIS IN UNITED STATES SOLDIERS STATIONED IN KOREA, 1967-1970: PROPHYLACTIC EFFICACY OF GAMMA GLOBULIN

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VIRAL hepatitis has always been a major medical problem in armies, particularly in time of war or of massing of troops in camps where sanitary conditions may be below standard. The logistic consequences of outbreaks of this disease, especially in times of conflict, have stimulated the Medical Corps of the Armed Forces of the United States to investigate all available details concerning its causes and to explore every possible means for its prevention. Since countless unsuccessful attempts to recover, identify, and cultivate the virus have failed, the preparation of a vaccine for active immunization has not been possible; therefore, the emphasis has shifted to passive immunization by means of immune gamma globulin prepared from pooled human sera. A number of encouraging reports have appeared concerning a preventive or alleviating effect of gamma globulin injections given during outbreaks of viral hepatitis in communities, schools, hospitals, and military units.[1-53] Most of these studies deal with a comparatively small number of cases, in which unstandardized human gamma globulin was used.

## Scope, Materials, and Methods

To test the prophylactic effect of immune gamma globulin on a large and significant scale this study was undertaken by the United States Army Medical Corps on United States Army personnel stationed in South Korea. This locality was chosen because of reports of numerous outbreaks of viral hepatitis, albeit of mild character and seasonal distribution, among members of our armed forces stationed in this area ever since the United States entered the Korean conflict. Some of these outbreaks have been well studied,[12, 26, 27, 37, 44] but the origins have not been traced satisfactorily. Poor sanitation has long been recognized, and contacts between soldiers and the native population have been suspected. The reports and references of Conrad[44] provide detailed information concerning the selection of Korea as the site of this study, the methods of control, the organization of the investigation, and the specifications of the gamma globulin employed.

Among 107,793 soldiers assigned to South Korea between May 1967 and August 1970, 43,065 received intramuscularly 10 ml. of placebo, a solution of sucrose potassium glutamate containing 2.5% human serum albumin; 64,728 soldiers were given intramuscularly 2 ml., 5 ml., or 10 ml. of immune gamma globulin. Approximately 65% of these soldiers received an identical second injection of either gamma globulin or placebo five to seven months later.

Four different lots of immune gamma globulin and serum albumin were purchased from the Hyland Division, Travenol Laboratories, Los Angeles, Calif. The sera had been obtained, processed, and tested in accordance with regulations of the Division of Biological Standards of the United States Public Health Service for immune serum gamma globulin and human serum albumin. All specimens had been taken from recently bled, paid donors in various areas of the United States. The antibody content of the final product of gamma globulin was tested against antigens to measles and polio. The levels of diphtheria antitoxin were measured and recorded for each lot. Studies of the Australia antibody content of the gamma globulin were performed and recorded.[44]

Passive immunization against infectious hepatitis should be provided before the onset of the incubation period, which lasts approximately 30 days.[54, 55] The presumed period of established passive immunity provided by the immune gamma globulin should extend from 30 to 200 days following the inoculation.[4, 13-16, 24, 25, 28-30] Presumably, each succes-

sive prophylactic inoculation should provide an identical period of protection or suppress the inflammatory process and produce long-lasting active-passive immunity resulting from the subclinical infection.[31] The date of the actual onset of the hepatitic process can be estimated by deducting the 30-day incubation period from the date of clinical appearance or of laboratory evidence of this disease.

All the soldiers stationed in Korea from May 1967 to August 1970 who developed clinical symptoms of infectious viral hepatitis were admitted for study to one of the two army hospitals in Korea. The diagnosis was made on the basis of the study of the history of the disease, the estimated length of the incubation period, clinical symptoms, and the results of the laboratory tests. In about 82% of all cases a needle biopsy of the liver was obtained, the patients having given voluntary consent. All biopsy specimens were examined and interpreted by Hans F. Smetana, without knowledge of the patient's background and history or of the clinical and laboratory data. The histopathologic findings and the diagnosis were recorded with all other data pertaining to the individual soldier, to be released only after the completion of the present investigation. None of these soldiers participating in this investigation had any prior knowledge concerning the purpose of these procedures.

The presence or absence of hepatitis-associated Australia antigen (HAA)[56-58] was determined by means of agar-gel immunoprecipitation and complement fixation,[59] 1) in the sera of 211 soldiers who had contracted clinical infectious hepatitis after receiving injections of placebo or gamma globulin and 2) in cases of hepatitis occurring in soldiers who had not received any previous inoculation.

## Analysis of Data and Comparison of Results

1) *Effects of Injection of gamma globulin and placebo. Comparison of data from uninoculated patients with hepatitis.* Between May 1967 and August 1970, 742 cases of infectious viral hepatitis occurred among the soldiers stationed in Korea. Of these, three groups were considered separately:

*Group A*: Cases occurring among the 43,065 soldiers who had received an injection of placebo on arrival in Korea and those who received a second injection five to seven months later. Two hundred forty-three soldiers in this group developed infectious viral hepatitis during this period.

TABLE I. VIRAL HEPATITIS IN UNITED STATES SOLDIERS STATIONED IN KOREA, 1967-1970: RESULTS OBTAINED AFTER INJECTION OF GAMMA GLOBULIN, AFTER INJECTION OF PLACEBO,* AND AFTER NO INJECTION

| *Type of injection* | *No. of soldiers* | *Cases of hepatitis* | | | | |
|---|---|---|---|---|---|---|
| | | *No. expected* | *No. occurring* | | | |
| | | | *After 1x* | *After 2x* | *Total* | *Per 1,000 soldiers* |
| 2 ml. gamma globulin 1x and 2x | 21,558 | 122† | 39 | 45 | 84 | 3.9 |
| 5 ml. gamma globulin 1x and 2x | 21,392 | 121† | 28 | 30 | 58 | 2.7 |
| 10 ml. gamma globulin 1x and 2x | 21,778 | 123† | 41 | 35 | 76 | 3.5 |
| Gamma globulin (total) | 64,728 | 365† | 108 | 110 | 218 | 3.4 |
| Placebo* 1x and 2x | 43,065 | Not known | 102 | 141 | 243 | 5.6 |
| No injection | 49,799† | Not known | | | 281 | 5.6 |
| Grand total | 157,592 | 889† | | | 742 | 4.7 |

*Solution of sucrose potassium glutamate containing 2.5% human serum albumin.
†Calculated according to the proportion after injection of the placebo.
1x = first injection, 2x = second injection.

*Group B*: Cases occurring among the 64,778 soldiers who had received an injection of either 2 ml., 5 ml., or 10 ml. of a 10% gamma globulin preparation on arrival in Korea and those who had received a second, identical injection five to seven months later. Two hundred eighteen soldiers in this group came down with viral hepatitis at varied intervals after the injections.

*Group C*: The 281 cases of viral hepatitis occurring among the 49,799 soldiers stationed in Korea during this period who had not received any placebo or gamma globulin prior to the occurrence of the hepatitis.

The soldiers who received gamma globulin, regardless of the dose or the timing of injections, showed a lower incidence of hepatitis than either those who had received placebos or those who had received no injections. This conclusion, although supported by statistically signifi-

cant differences in the gross figures, must be accepted with caution. This study was massive, but it lacks incisiveness because of the uncertainty of some of the premises on which it is based. Chief among these is the lack of solid evidence that the "anti-hepatitis gamma globulin" which was used actually contained an effective level of antibody against viral hepatitis. The differences in incidence were statistically significant and are evidence of some degree of prophylactic efficacy of the gamma globulin preparations used in this study (Table I). Differences in the protection afforded by the administration of different amounts of gamma globulin were not impressive.[60]

2) *The relation of the number of days after arrival in Korea and the dates of injection of placebo or gamma globulin to the number of cases of hepatitis and the relation of the number of days between these injections and time of onset of the disease.*

The period of 30 to 200 days after the prophylactic injection of gamma globulin is considered to offer the greatest protection against the acquisition of hepatitis. Therefore, the number and dates of injections of gamma globulin were studied in relation to the time of onset of the disease (date of clinical evidence minus 30-day incubation period). These results were compared with the effects of placebo injections and the incidence of hepatitis among the soldiers who had not received any injections. The percentages of the number of inoculations and of the total number of cases in these two groups were used as means of comparison.

The data presented in Table II indicate that of the 43,065 soldiers in Group A, 243 who had received a total of 384 inoculations of placebo contracted infectious hepatitis. Of the 384 inoculations, 199 (51.8%) had been given between 0 and 200 days prior to the onset of hepatitis. Of those who had received these 199 inoculations, 84 soldiers (34.6%) developed infectious hepatitis during the period of 0 to 200 days.

Of the 64,728 soldiers in Group B, 218 who had received a total of 328 injections of gamma globulin acquired infectious hepatitis. Of the 328 injections, 168 (51.2%) had been given between 0 and 200 days prior to the onset of infectious hepatitis. Of those who had received the 168 inoculations, 82 soldiers (37.6%) developed infectious hepatitis during the period of 0 to 200 days after the injection.

Two hundred eighty-one of an estimated 50,000 soldiers who had

TABLE II. THE PROPHYLACTIC EFFICIENCY OF GAMMA GLOBULIN GIVEN TO UNITED STATES SOLDIERS STATIONED IN KOREA, 1967-1970: NUMBER OF DAYS AFTER ARRIVAL IN KOREA, INJECTION OF PLACEBO, OR INJECTION OF GAMMA GLOBULIN AND THE RELATION OF THESE TO THE NUMBER OF CASES OF VIRAL HEPATITIS AND THE NUMBER OF DAYS BEFORE THE ONSET OF HEPATITIS

| *Injections* (No.) | (%) | *Days between injection and onset* of hepatitis* (No.) | *Days between arrival in Korea and onset* of hepatitis* (No.) | *Cases of hepatitis* (No.) | (%) | *Soldiers* (No.) |
|---|---|---|---|---|---|---|
| | | | *Group A. (Placebo)* | | | |
| 20 | 5.2 | −28† to 0 | | 4 | 1.6 | 43,065 |
| 80 | 20.8 | 0 to 100 | | 21 | 8.6 | |
| 99 | 25.8 | 100 to 200 | | 59 | 24.4 | |
| 199 | 51.8 | 0 to 200 | | 84 | 34.6 | |
| 106 | 27.6 | 200 to 300 | | 92 | 37.8 | |
| 55 | 14.4 | 300 to 400 | | 47 | 19.3 | |
| 24 | 6.2 | 400 to 801 | | 20 | 8.2 | |
| Total 384 | 100.0 | −28† to 801 | | 243 | 99.9 | |
| | | | *Group B. (Gamma globulin)* | | | |
| 15 | 4.6 | −27† to 0 | | 6 | 2.7 | 64,728 |
| 64 | 19.5 | 0 to 100 | | 27 | 12.4 | |
| 89 | 27.1 | 100 to 200 | | 49 | 22.5 | |
| 168 | 51.2 | 0 to 200 | | 82 | 37.6 | |
| 89 | 27.1 | 200 to 300 | | 73 | 33.5 | |
| 45 | 13.7 | 300 to 400 | | 39 | 17.9 | |
| 26 | 7.9 | 400 to 701 | | 24 | 11.0 | |
| Total 328 | 99.9 | −27† to 701 | | 218 | 100.0 | |
| | | | *Group C. (No injection)* | | | |
| | | | −7† to 0 | 1 | 0.4 | 50,000‡ |
| | | | 0 to 100 | 28 | 10.0 | |
| | | | 100 to 200 | 65 | 23.1 | |
| | | | 0 to 200 | 94 | 33.5 | |
| | | | 200 to 300 | 87 | 31.0 | |
| | | | 300 to 400 | 67 | 23.8 | |
| | | | 400 to 1,100 | 33 | 11.7 | |
| Total | | | −7† to 1,100 | 281 | 100.0 | |

*Date of clinical evidence minus 30-day incubation period.
†The onset of hepatitis occurred before or during the incubation period, indicating that the disease was probably acquired prior to the arrival of these soldiers in Korea.
‡Estimated.

been stationed in Korea between May 1967 and August 1970 and had not been inoculated with either placebo or gamma globulin developed infectious hepatitis; of these, 94 soldiers (33.5%) had arrived in Korea between 0 and 200 days before the onset of this disease.

The data presented in Table II indicate that infectious hepatitis tends to occur at about the same period of time in the three groups, uninfluenced by the number of prior inoculations of either placebo or gamma globulin. The period of time spent in Korea seems important; the number of days after arrival for Group C corresponds with the time between the first inoculations and the onset of hepatitis in the other groups. The incidence of hepatitis occurring from 0 to 200 days following injection of placebo, injection of gamma globulin, and arrival in Korea without any treatment are virtually the same. The incidence of disease is not influenced by the percentage of inoculations given prior to the appearance of the hepatitis.

It is of interest that the incidence of disease with placebo and gamma globulin injections corresponds to a similar percentage of cases of hepatitis occurring in other populations within a similar period of time. According to these data, the present study does not demonstrate any reliable period of protection against the acquisition of infectious hepatitis between 0 and 200 days after the injection of gamma globulin.

### Comparison of Clinical, Laboratory, and Histopathologic Data on Hepatitis in the Three Groups of Soldiers

The results of this survey are presented in Table III, which shows the number of days elapsed between arrival in Korea or between the first injection of either placebo or gamma globulin and the date of hospitalization for hepatitis. (Cases of hepatitis which occurred among soldiers who had not received injections are included.) It also shows the length of stay in the hospital; the number of days between symptoms and hospitalization or biopsy; the percentage of soldiers presenting cutaneous or scleral jaundice or both; the average, maximum, and minimum values of units of serum glutamic oxaloacetic transaminase (SGOT); and the duration of clinical disease.

Although the table shows divergences between some of the clinical and laboratory findings for patients in the same and in different groups, this may be explained 1) by variations in the time elapsed between onset of the disease and the date at which the patient came to observation or

TABLE III. COMPARISON OF CLINICAL, LABORATORY, AND PATHOLOGIC DATA FOR THREE GROUPS OF SOLDIERS DEVELOPING VIRAL HEPATITIS WHILE STATIONED IN KOREA, 1967-1970

| *Cases (No.)* | *Days between arrival or 1st injection and onset* of hepatitis* | *(No.)* | *Days of hospitalization (No.)* | *Symptomatic days before: Hospitalization (No.)* | *Biopsy (No.)* | *Clinical diagnosis* | *Laboratory findings* | *Cases with jaundice: Cutaneous (%)* | *Sclera (%)* | *SGOT* | *Duration of illness (weeks)* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *Group A. (Placebo)* | | | | | | | |
| 243 | *Average* | 180 | 26 | 6 | 13 | Viral | Consistent with | 57 | 78 | 876 | 4 to 5 |
| | *Maximum* | 414 | 63 | 19 | 39 | hepatitis | hepatitis | | | 1,260 | 6 |
| | *Minimum* | 58 | 9 | 1 | 5 | | | | | 355 | 2 |
| | | | | *Group B. (Gamma globulin)* | | | | | | | |
| 218 | *Average* | 180 | 25 | 6 | 14 | Viral | Consistent with | 57 | 56 | 715 | 3 to 4 |
| | *Maximum* | 311 | 44 | 15 | 24 | hepatitis | hepatitis | | | 1,130 | 6 |
| | *Minimum* | 91 | 10 | 2 | 6 | | | | | 107 | 2 |
| | | | | *Group C. (No injection)* | | | | | | | |
| 281 | *Average* | 272 | 28 | 8 | 13 | Viral | Consistent with | 35 | 66 | 972 | 3 to 4 |
| | *Maximum* | 627 | 86 | 33 | 43 | hepatitis | hepatitis | | | 1,835 | 6 |
| | *Minimum* | 70 | 10 | 2 | 3 | | | | | 167 | 2 |
| | | | | *All cases of viral hepatitis* | | | | | | | |
| 742 | *Average* | 211 | 26 | 7 | 13 | Viral | Consistent with | 49 | 67 | 921 | 3 to 4 |
| | *Maximum* | 451 | 64 | 22 | 35 | hepatitis | hepatitis | | | 1,408 | 6 |
| | *Minimum* | 73 | 10 | 2 | 5 | | | | | 531 | 2 |

SGOT=Serum glutamic oxaloacetic transaminase.
*Date of clinical evidence minus 30-day incubation period.

2) by difference in the severity of individual cases. All patients showed clinical jaundice of skin, sclerae, or both. There were no significant differences in the findings by which the three groups could be separated and identified. The only significant differences between cases represented variants of the histopathologic picture caused by differences in duration or severity of the disease. In all three groups all alterations observed in the liver biopsies were consistent with known stages of hepatitis.

### Presence of Australia Antigen in Relation to the Time of Onset of Hepatitis (With or Without Previous Injection)

Table IV shows the results of tests for the presence or absence of Australia antigen (AA) in 211 cases of infectious hepatitis. The results are shown in relation to the time of onset of the disease and the date of arrival of the soldiers in Korea or the dates of injection of placebo or gamma globulin. The presence of this substance within, before, or after the period of 30 to 200 days after inoculation or after arrival in Korea, i.e., the period of maximal protection by gamma globulin against infectious viral hepatitis, is also indicated for each group.

In the group that had received injections of gamma globulin, 15 (17%) of the 87 soldiers with hepatitis who were tested were positive for AA. Of these, five positive cases (6%) were found in blood samples taken 30 to 200 days after inoculation; in 10 cases (11%) AA was present in sera taken outside this period. After injections of placebo there were 12 positive cases (14%) among 84 tests performed. Three occurred within the period of 30 to 200 days after injection, nine cases (11%) were found outside this period. The smallest number of positive cases of AA occurred in the group of hepatitis patients who had not received any previous injections of either placebo or gamma globulin. Among the 40 patients tested, all three positive cases (8%) were found in samples of blood taken from soldiers during the period of 30 to 200 days after their arrival in Korea.

In summary, of a total of 211 tests comprising all three groups of cases of infectious hepatitis, 30 (14%) were positive and 181 (86%) were negative. In none of these 30 positive cases was there a history of blood transfusion prior to the onset of hepatitis. Eleven positive cases (5%) had occurred within the 30-to-200-day period after arrival in Korea or after the first injection of placebo or gamma globulin; 75

TABLE IV. PRESENCE OF AUSTRALIA ANTIGEN (AA) IN CASES OF THE HEPATITIS OCCURRING IN THREE GROUPS OF SOLDIERS STATIONED IN KOREA FROM 1967 TO 1970 IN RELATION TO DATE OF ARRIVAL IN KOREA OR DATE OF INJECTION OF GAMMA GLOBULIN OR PLACEBO

| *Cases of hepatitis* | | | | | | | *Cases of hepatitis occurring* | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | *0 to 200 days after arrival or injection* | | | | *Before or more than 200 days after arrival or injection* | | | |
| *Total (No.)* | *Tested for AA (No.)* | *(%)* | *AA+ (No.)* | *AA+ (%)* | *AA− (No.)* | *AA− (%)* | *AA+ (No.)* | *AA+ (%)* | *AA− (No.)* | *AA− (%)* | *AA+ (No.)* | *AA+ (%)* | *AA− (No.)* | *AA− (%)* |
| | | | | | | | *Group A. (Placebo)* | | | | | | | |
| 243 | 84 | 100 | 12 | 14 | 72 | 86 | 3 | 4 | 12 | 14 | 9 | 11 | 60 | 71 |
| | | | | | | | *Group B. (Gamma globulin)* | | | | | | | |
| 218 | 87 | 100 | 15 | 17 | 72 | 83 | 5 | 6 | 27 | 31 | 10 | 11 | 45 | 52 |
| | | | | | | | *Group C. (No injection)* | | | | | | | |
| 281 | 40 | 100 | 3 | 8 | 37 | 92 | 3 | 8 | 36 | 90 | 0 | 0 | 1 | 2 |
| Total | 211 | 100 | 30 | 14 | 181 | 86 | 11 | 37 | 75 | 41 | 19 | 63 | 106 | 59 |

AA+=Australia antigen present, AA−=Australia antigen not present.

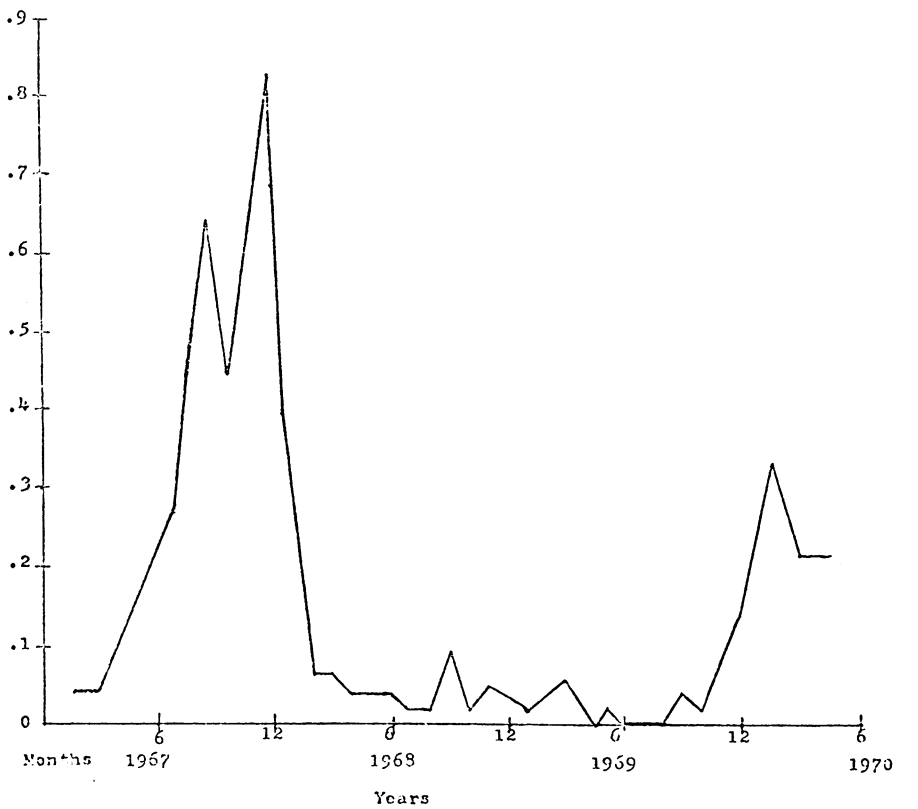


Fig. 1. Incidence of viral hepatitis in United States soldiers stationed in Korea from 1967 to 1970. Estimated number of soldiers who received no injections: 50,000; total number of cases of hepatitis: 281. The number of cases per 1,000 soldiers is given on the vertical axis.

cases showing negative results (36%) had occurred within the same period of time. Nineteen positive cases (9%) were observed among the 125 instances of hepatitis that developed outside this period of time, while 106 cases (50%) were negative for AA. The presence of AA in 30 soldiers (14%) among 211 cases of viral hepatitis present problems in interpreting the origin of this feature in the sera of these soldiers.

### Distribution of Infectious Viral Hepatitis in Relation to Inoculation and the Absence of Inoculation, 1967-1970

In order to study the over-all distribution of 742 instances of infectious viral hepatitis that had developed either with or without previous injection of placebo or gamma globulin among 157,592 United States

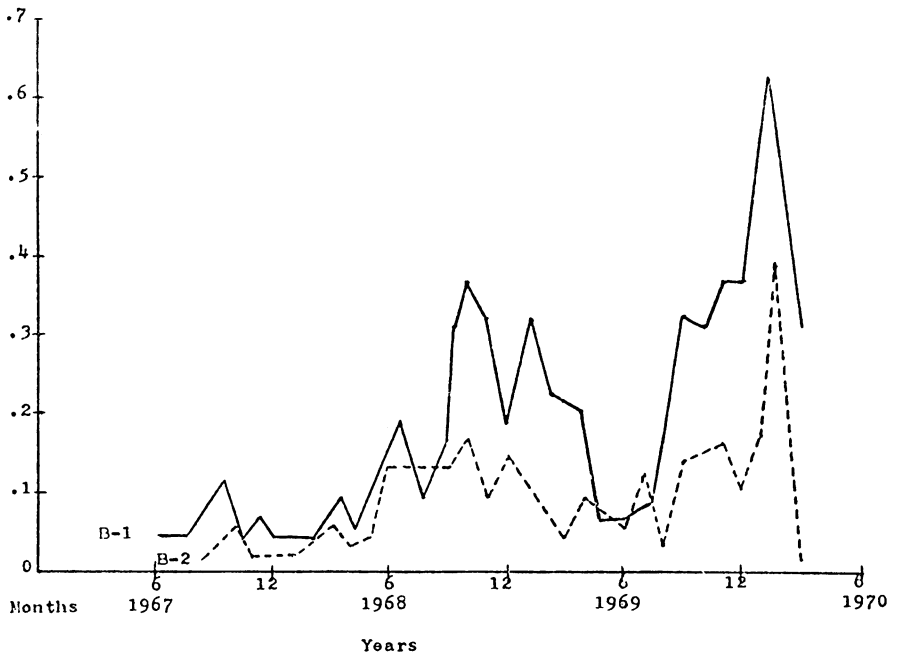


Fig. 2. Incidence of viral hepatitis in United States soldiers stationed in Korea from 1967 to 1970 who received injections of placebo or gamma globulin. Of the 43,065 soldiers who received injections of placebo, 243 developed hepatitis (solid line, B-1). Of the 64,728 soldiers who received injections of gamma globulin, 218 developed hepatitis (broken line, B-2). The number of cases per 1,000 soldiers is given on the vertical axis.

soldiers stationed in Korea between May 1967 and August 1970, graphs were prepared of all the cases per 1,000 soldiers within the individual groups in order to reveal similarities or differences.

Figure 1 is based on cases in which no injection had been given; it comprised 281 instances. The graph has a maximum during the fall and winter of 1967, followed by much smaller numbers of cases during 1968 and 1969 and a final moderately high peak during the winter of 1969-1970. The over-all shape of the graph resembles those presented by Gauld,[12] by Conrad,[37, 44] and by Rowland and Skone[45] in their studies of the epidemiology of hepatitis in Korea during 1950-1955 and 1967-1970 and of similar epidemics that occurred in various parts of the world from 1950 to 1970. The total incidence of hepatitis in the group represented in Figure 1 was 5.6/1,000 soldiers per year.

The solid line in Figure 2 is based on 243 cases of hepatitis that developed in Group B-1 after one and two injections of placebo. Only

a few cases occurred during the summer of 1967. The number rose to a moderate height during the fall and winter of 1968-1969 and declined to a low level during the summer of 1969. The number of cases rose to a maximum during the winter of 1969-1970. The total incidence of hepatitis in the group was 5.6/1,000 soldiers per year.

Cases of hepatitis following injection of gamma globulin (218 cases) are represented by the broken line B-2 in Figure 2, which presents similarities to the graph of those given placebos in that only a few cases of hepatitis were registered in 1967. The number of cases in this group increased during the fall and winter of 1968-1969 and reached a maximum during the winter of 1969-1970. The incidence was 3.4/1,000 soldiers per year.

Figure 3 is a combined graph of all the 742 cases of hepatitis that occurred in the soldiers under study. It presents an impressive picture. The number of cases increased in the fall and winter of 1967 and 1968, reaching a maximum during the fall and winter of 1969 and 1970. A decline occurred during the spring and summer of 1968 and 1969 and the spring of 1970. The incidence in this group was 4.7/1,000 soldiers per year. Figure 3 expresses the over-all, seasonal distribution of infectious viral hepatitis among the soldiers stationed in Korea from 1967 to 1970, irrespective of injection of placebo or gamma globulin or the absence of previous medication.

## Importance of the Correct Diagnosis of Viral Hepatitis

Since the virus of hepatitis has not been cultivated, indirect means must be applied to justify the diagnosis of the disease. From the point of view of the pathologist, the histopathologic alterations in the liver remain the most important basis for confirmation of the clinical and laboratory diagnosis.[61-69] Since open surgical biopsies often produce artifacts in hepatic tissue because of surgical trauma,[68] needle biopsy is preferred and is employed widely. In the present investigation about 82% of all the cases diagnosed clinically as viral hepatitis were confirmed by histologic studies. Cases were recorded as hepatitis without biopsy only if clinical and laboratory findings—and the clinical course of the disease—were consistent with those obtained in established cases in the present series. Anicteric hepatitis and drug-induced liver disease were not registered, as they rarely satisfy the histopathologic criteria of viral hepatitis and there is doubt concerning any implied histopathologic

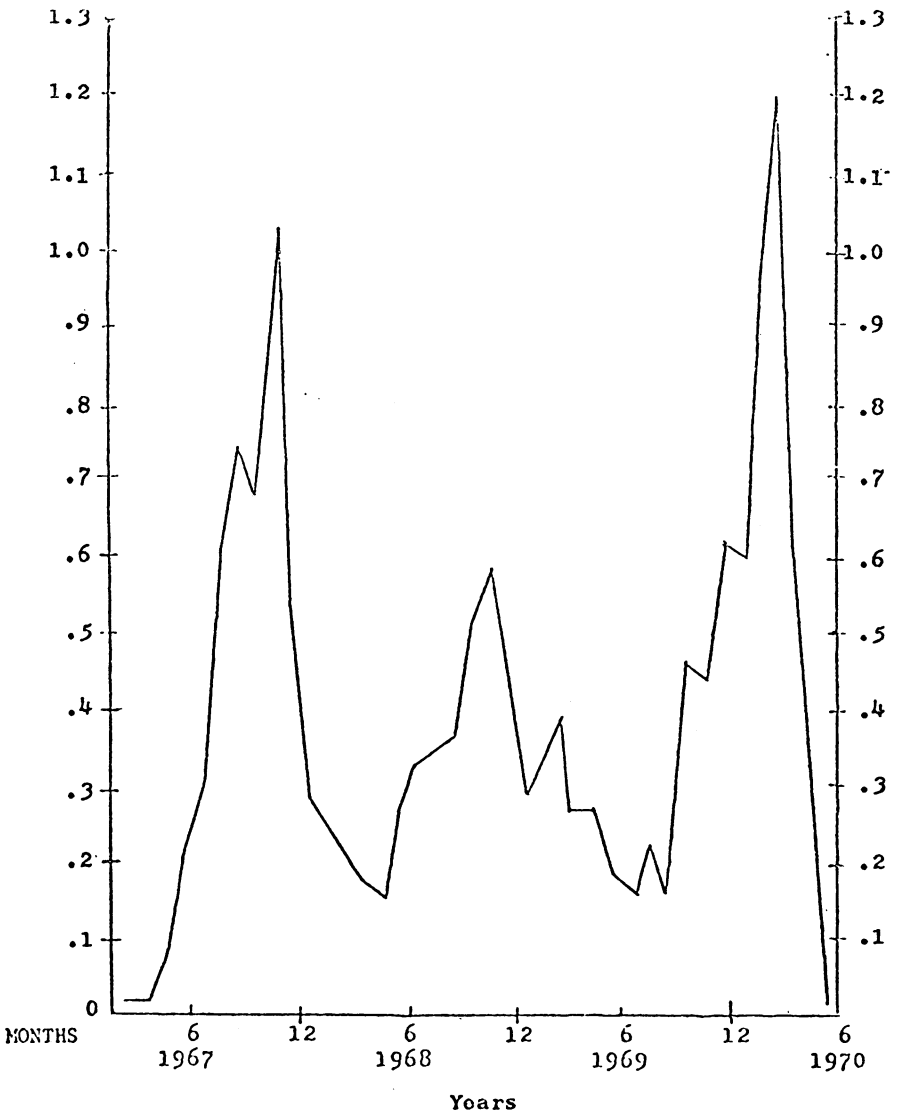


Fig. 3. Seasonal distribution of 742 cases of viral hepatitis which occurred in 157,592 United States soldiers stationed in Korea from 1967 to 1970. Combined data for soldiers who had received injections of gamma globulin (218) or placebo (243) and soldiers who received no injections (281). The number of cases per 1,000 soldiers is given on the vertical axis.

consequences of anicteric hepatitis. This statement is made despite extensive statements of opposite tenor in the literature. It is based on the study of a large group of registered cases of hepatitis, including follow-up observations made during the past 25 years at the Armed Forces Institute of Pathology in Washington, D.C.[69] Although the histopathologic diagnosis of hepatitis has been described well, the changes seen in individual cases may be extremely variable, depending on the degree of involvement and on the duration and the severity of the process.[61-67]

## Reliability of Premises on Which the Prophylactic Use of Immune Gamma Globulin Is Based

The most important factor governing the prophylactic effectiveness of the immune gamma globulin used in this investigation lies in its supposed ability to neutralize the specific viral antigen of infectious viral hepatitis by the action of its specific antibodies. Because it is as yet impossible to cultivate the virus of viral hepatitis, the production, isolation, and identification of the specific antibodies in the gamma globulin of the preparations used in this investigation cannot as yet be realized. Therefore, the brilliant and reliable procedures of Landsteiner, Heidelberger, Kendall, Tiselius, Kabat, and others for recognition and isolation of specific antibodies to specific bacterial antigens in the gamma globulin of specific antisera[70-82] cannot be applied to the problem of the specific antigen and antibodies of viral hepatitis.[83] The results of testing the gamma globulin used in this study for antibodies other than those directed specifically toward the antigen of viral hepatitis (e.g., measles, polio II, or diphtheria) cannot *a priori* be considered decisive as to their proposed effectiveness against viral hepatitis. Recently proposed methods of binding the unknown quantity of antigen of an antiserum to a known amount of antibody for subsequent analysis are indeed promising but seem rather complicated for practical purposes. Moreover, some of these methods were not available at the time of our Korean experiment.

According to Heidelberger,[83] the studies by Porter[84] and Edelman[85] promise an eventual solution of this important problem. The only method available at the time of the study was the actual testing of each individual preparation of immune gamma globulin against a viral hepatitis antigen of proved potency, in field trials during outbreaks of hepatitis, in human volunteers, or in responsive subhuman primates before its final use as a prophylactic. Since this was not done in the present

investigation, the actual potency of the immune gamma globulin used cannot be considered established.

Results of numerous clinical and laboratory studies using injections of immune gamma globulin obtained from infectious hepatitis patients have demonstrated significant differences in the effectiveness of various preparations in the prevention of hepatitis. The variation is attributed to different methods of preparation, lapse of time after isolation, fragmentation of gamma globulin, vulnerability of gamma globulin to oxidation, size of dose, type of population, and other conditions.[1-7, 9-11, 16-18, 21-23, 28, 31-33, 38, 39, 43, 44, 47-53] Mosely et al.[33] place the greatest weight on the antibody levels of the preparations; this is revealed by preliminary assays.

The evaluation of the effect of the number and dates of inoculations of gamma globulin used in the present study on the prevention of infectious hepatitis shows no significant percentile differences between injections of placebo and of gamma globulin (see Table II). This uncertainty concerning the reliability of the basic factors which determine the effectiveness of the prophylactic use of immune gamma globulin against hepatitis reduces the credibility of the results of this entire study, including the problematic role of the safety period of 0 to 200 days following the injection of gamma globulin.

The importance of the presence of AA in relation to infectious viral hepatitis is difficult to state in the present study. Some of the earlier reports relate the presence of AA in cases of viral hepatitis to an active or past infection with the virus of hepatitis B.[58, 86] The epidemic viral hepatitis that occurred among United States soldiers stationed in Korea after the Korean conflict has been studied since 1950[12] and has been considered a characteristic example of type A infectious hepatitis without any marker.[46, 87]

The presence of HAA in 14% of the 211 cases of hepatitis tested for this antigen seems rather surprising, even if HAA-positive hepatitis can be transferred by the oral route as well as by means other than blood transfusion.[40, 88] Since the discovery of the relation between hepatitis and HAA occurred some time after Gauld's study,[12] any association which may have existed between HAA and this form of infectious hepatitis at the time of his investigation will remain unknown.

An enormous amount of literature concerning AA has accumulated since Blumberg's original publication,[56, 57] and some of it appears con-

tradictory. Is infectious hepatitis caused by virus A one and the same disease as serum hepatitis caused by virus B? Is the presence of AA in the serum in infectious hepatitis an indicator of the presence of virus B?[89] While AA is considered to be associated specifically with serum hepatitis, infectious hepatitis is not identifiable by AA in the serum of patients.[89] Are infectious viral hepatitis and transfusion hepatitis two distinctively different diseases[58, 86] on clinical, epidemiological, and immunological grounds? Are they one and the same disease in principle, with different manifestations of symptoms, incubation time, and severity, due to difference in the portal of entry of the virus? While both forms may be associated with AA,[90-92] does virus B represent a modification of virus A, produced by metabolic and immunologic processes during prolonged survival in the host who has viremia and alimentary disease, so that the virus of serum hepatitis becomes an entirely different artificial infective agent?[93] Does any previous infection with hepatitis due to type A virus confer any immunity against virus B infection or vice versa?[40, 94] These are some of the areas of disagreement among authors who deal with this problem which will have to be clarified by experiment and, probably, by the use of responsive primate models. Modes of infection with AA, exposure to HAA, possible prevention of virus B hepatitis, the cause of the long incubation period of virus B hepatitis, and other problems were discussed by Sheila Sherlock.[95]

The question of whether AA actually represents the virus of viral hepatitis has been brought up repeatedly. Although actual proof of this possibility has not been furnished, many authors believe that AA appears to be related to the infectious agent of viral hepatitis.[93-104]

Our analysis of the clinical, laboratory, and histopathologic data of the Korean cases of hepatitis with or without positive AA—after injection of placebo or gamma globulin, or without inoculations prior to the onset of hepatitis—in regard to a number of factors such as dates of onset in relation to dates of injections and of arrival in Korea revealed no significant difference and no other significant information (see Table IV). An experimental study of clinical, laboratory, and histopathologic features, probing the possible infectivity of purified AA in two laboratory-bred young chimpanzees (to avoid contact with chimpanzees harboring "natural" chimpanzee hepatitis) also failed to produce clinical, laboratory, or histopathologic evidence of viral hepatitis within three months.[105]

In a recent article by Vittal et al.[106] asymptomatic hepatic disease was reported in 30 blood donors who had hepatitic antigenemia; three of these donors were heroin addicts. Laboratory examination and liver biopsy yielded evidence of mild hepatic involvement, but the changes were not characteristic of viral hepatitis.

Interesting and important reports dealing with various phases of virus A and virus B hepatitis, AA, and transfusion hepatitis have been presented.[107-125]

Sera exhibiting positive AA have been reported repeatedly as "drug hepatitis;"[126] presumably these were cases in which contaminated needles had beeen used by several persons. In some of these cases several attacks were described and were attributed to viral hepatitis. Does virus B hepatitis confer immunity to subsequent attacks by the same virus? Is "drug hepatitis" due to a reactive process in the liver related to detoxifying action on injected drugs as well as to the reaction to introduced contaminants?

Although Grady[127] believes that "the serendipitous aspects of Blumberg's findings (Australia antigen in mongolism, Down's syndrome, leukemia, hepatitis, chronic hepatitis, cirrhosis of the liver, lepromatous leprosy, etc.,) hold the center stage now, in the long run, however, the genetic aspects may prove to be equally interesting."

The problem of the importance of AA in relation to hepatitis, particularly hepatitis of the infectious A type, cannot be evaluated and clarified in this study of the viral hepatitis in United States soldiers stationed in Korea as influenced by the prophylactic administration of immune gamma globulin.

## Evaluation of the Efficacy of Gamma Globulin in Prevention of Viral Hepatitis

As stated above, the immune gamma globulin employed in this study had been tested for antibodies of measles, polio II, levels of diphtheria antitoxin, and Australian antibodies. Its prophylactic value was then tested in a large number of soldiers stationed in an area of endemic hepatitis. The results were compared with those obtained in a large number of controls injected with an innocuous placebo as well as in a large group of soldiers who had not received either placebo or gamma globulin and thereby constituted a second control group.

Particular attention was paid to the effectiveness of immune gamma

globulin injected within the period of 0 to 200 days prior to the onset of hepatitis—presumably representing the best available prophylactic against hepatitis. All soldiers with or without inoculation who came down with hepatitis were studied clinically and by laboratory methods for evidence of hepatitis, and the clinical diagnosis was confirmed by needle biopsy of the liver in 82% of all cases. Graphs of all cases of hepatitis in the three groups were then studied for similarities and differences.

## Discussion

It should be kept in mind that all results and conclusions of the present investigation apply only to this particular preparation of immune gamma globulin and not to the over-all problem of immune gamma globulin used as a prophylactic means for preventing viral hepatitis.

This study represents one of the most extensive human experiments ever conducted in a controlled population and was undertaken in an effort to evaluate the efficacy of a prophylactic measure against one of the major infectious diseases of man—viral hepatitis. The urgency of the problem required that the study be launched even in the presence of almost insurmountable difficulties. The causative agent of viral hepatitis has never been isolated and cultured, the method of natural transmission is still obscure, no dependable diagnostic test is available as yet, no reliable animal model has been developed, and no solid epidemiologic theory has been established. The relation of the disease to AA is still veiled and tentative, the protective effect of gamma globulin per se remains unknown, the frequency of asymptomatic carriers of the disease in the general population has not been established satisfactorily, and little is known about the natural and acquired immunity of the general population. In addition, the effect of repeated injections of gamma globulin for prevention of hepatitis has not been evaluated experimentally. Despite all these uncertainties, the study was conducted to test—on a pragmatic level—whether administration of immune gamma globulin obtained through commercial channels in the United States from the pooled blood of paid donors could reduce the incidence of this disease in military personnel stationed abroad or at least could alleviate the effects of hepatitis in soldiers stationed in Korea, in an area known to have a high incidence of the endemic disease.

The results of this interesting and important investigation must

be evaluated as well as possible despite the unreliability of the premises on which the conclusions must be based. Because of the unreliability of the basic premises, standard methods of statistical evaluation may or may not lead to sound decisions.

## Conclusions

Prophylatic injections of commercial gamma globulin given for the prevention of infectious viral hepatitis were followed by a moderate but significant reduction in the number of cases of infectious hepatitis in United States soldiers stationed in an area of endemic hepatitis, South Korea, from May 1967 to August 1970 as compared with controls. The actual cause of this reduction has not been established. It may be related to local seasonal circumstances, to waves of increased and decreased activity of the endemic disease, to the length of stay of soldiers within the area of the endemic disease, or to increased contact between the soldiers and the local population.

The uncertain prophylactic properties of the gamma globulin were demonstrated by the apparent ineffectiveness of this substance in preventing hepatitis, by the close similarity of the effect of placebo injections, and by the time element of residence in Korea. There was no significant decline in the infection during the supposed period of greatest protection, i.e., from 0 to 200 days after the injection of gamma globulin. Although a possible prophylactic effect of the gamma globulin cannot be disregarded entirely, the results of detailed analysis make it equally improbable that the reduction in the number of cases of hepatitis can be attributed to the action of the gamma globulin.

Histopathologic studies of needle biopsies of the liver in cases of hepatitis following injection of gamma globulin did not yield evidence of a prophylactic, ameliorating, or protective effect of gamma globulin, or any differences from the results of placebo injection or of no injection.

Evidence of hepatitis—proved by clinical symptoms, laboratory findings, and histopathologic evaluation of needle biopsies of the liver —occurred in the presence or absence of demonstrable AA in sera of 211 cases of hepatitis tested for this substance. There was no obvious relation to injection of gamma globulin or placebo. This result also was found in some of the cases of hepatitis that had occurred in soldiers who had not received any previous injections.

The uncertainty of any demonstrable prophylactic protection by the gamma globulin used in this study, the lack of the assumed protection within the assumed best period of protection (from 0 to 200 days following the injection of gamma globulin), and the lack of the effect expected from multiple injections of gamma globulin make any definitive application of the results of this study difficult if not impossible.

In order that a similarly designed experiment should yield definitive practical results, a reliable, quantative method for evaluation of the specific antibodies of the gamma globulin to be employed will have to be developed. Its actual effect will have to be tested in field trials on human volunteers or responsive primate models, with proved potent hepatitis antigen being used as the infecting agent.

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