

process. Careful supervision during these periods is important, as was recently stressed by Macpherson.⁵

A controversial question concerns the wisdom of continuing lactation after the breast infection has been controlled. With penicillin therapy it is possible to maintain lactation through and following the infection. That this is not desirable is illustrated by 3 of our patients who gave the history of having received penicillin for a minor breast infection during their immediate postpartum period. All apparently recovered and continued to nurse their babies after going home. When first seen by us approximately two weeks later, each had developed a severe mastitis in the contralateral breast, which responded well to the penicillin program herein described.

Dosage.—A factor of major importance in the treatment of staphylococcal infections in general is adequate dosage of penicillin. The staphylococcus notably becomes penicillin fast under inadequate dosage.⁶ The dosage used in the present series of cases has been sufficient. Clinical remission is apparently complete in most patients after sixty hours of treatment. Hence it is felt important to continue the medication until the full course has been administered to obviate the possibility of reactivation because of bacterial resistance to penicillin. The tapering off period of 15,000 Oxford units every three hours for the last two days of treatment is good insurance against this complication.

Breast Abscess.—Systemic penicillin may be of value in cases of frank abscess formation by preventing the extension of infection to adjacent lobes. Fraser⁷ reported 15 cases treated by aspiration and instillation of penicillin into the abscess cavity, with resolution without drainage in only 3 cases. He suggested using penicillin for its systemic effect at an earlier stage, feeling that local treatment offered little. Penicillin will not replace adequate incision and drainage of an abscess.

CONCLUSIONS

1. Twenty-four patients suffering from acute puerperal mastitis were treated with penicillin. All resolved without abscess formation. Eight hundred and forty thousand Oxford units was administered to each patient under a five day plan of treatment consisting of 25,000 Oxford units every three hours for seventy-two hours, then 15,000 Oxford units every three hours for forty-eight hours.

2. Sulfonamide therapy, because of its relative ineffectiveness, is not recommended as a substitute for early institution of penicillin treatment in acute staphylococcal puerperal mastitis.

5. Macpherson, A. I. S.: Acute Puerperal Breast Abscess: Clinical Observations on Its Etiology and Suggested Method of Treatment, Year Book of Obstetrics and Gynecology, 1944, Greenhill, Year Book Publishers, Chicago.

6. Rammelkamp, C. H., and Maxon, T.: Resistance of Staphylococcus Aureus to the Action of Penicillin, Proc. Soc. Exper. Biol. & Med. 51: 386-389 (Dec.) 1942. Lyons, C.: Penicillin Therapy of Surgical Infections in the U. S. Army, J. A. M. A. 123: 1007-1018 (Dec. 18) 1943.

7. Fraser, D. B.: Local Treatment of Breast Abscess with Penicillin, Brit. M. J. 1: 523-524 (April 15) 1944.

Effect of War and Depression.—The status of the civilian changes during war to a part time soldier. Due to well entrenched habit formation, he is either consciously or unconsciously trying to lead a normal life, but at any time he may find himself the object of an attack or playing an active part in meeting enemy attack. In addition, he is constantly confronted by necessary war regulations which restrict his peacetime civil liberties.—Davis, John E.: Principles and Practice of Rehabilitation, New York, A. S. Barnes & Co., Inc., 1943.

PREVENTION OF INFECTIOUS HEPATITIS WITH GAMMA GLOBULIN

MAJOR W. P. HAVENS JR.

MEDICAL CORPS, ARMY OF THE UNITED STATES

AND

JOHN R. PAUL, M.D.

NEW HAVEN, CONN.

In January 1945 Stokes and Neefe¹ published the first report of the use of human gamma globulin in the prevention of infectious hepatitis. Results indicated that this prophylactic measure was effective and that the use of this substance in infectious hepatitis compared favorably with its use in measles.

In the present report it is our purpose to describe another instance of the effective use of gamma globulin as a prophylactic measure in an institutional epidemic of infectious hepatitis. The outbreak to be described occurred in a Catholic home for children in New

TABLE 1.—Grouping of Institutional Population

Group	Number in Group	Basis of Selection	Inoculated
A	97	Susceptible.....	Yes
B	155	Susceptible.....	No
C	47	"Immunes" (previously ill).....	No
D	39	Adults.....	No

TABLE 2.—Dosage Employed

Child's Weight, Pounds	Gamma Globulin Injected, Cc.
40-79.....	5
80-119.....	8
120+.....	10

TABLE 3.—Comparison of Rates in Groups A and B

Group	Number	Jaundice		? Hepatitis	
		Cases	Per Cent	Cases	Per Cent
A (inoculated).....	97	2	2	6	6
B (control).....	155	36	23	17	11

Haven.² This home had on Jan. 20, 1945 a population of 299 children (90 per cent of whom were between the ages of 6 and 16) and 39 adults. During the period between Nov. 5, 1944 and April 27, 1945, 53 cases of infectious hepatitis with jaundice and 56 cases of questionable hepatitis without clinical jaundice occurred at the home (chart 1). In the latter group of non-icteric cases the diagnosis was often somewhat indefinite. It was based on a sequence of symptoms similar to those usually found in the early stage of hepatitis with jaundice; namely, an acute onset with fever of 101-103 F., headache, nausea and vomiting. Generalized aches and pains were common, and pain in the abdomen was present in about half of these cases. The average duration of fever in these nonicteric cases was two days

From the Section of Preventive Medicine, Yale University School of Medicine.

This investigation was aided in part by the Commission on Neurotropic Virus Diseases, Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, Preventive Medicine Service, Office of the Surgeon General, U. S. Army.

1. Stokes, J., and Neefe, J. R.: The Prevention and Alleviation of Infectious Hepatitis by Gamma Globulin, J. A. M. A. 127: 144 (Jan. 20) 1945.

2. This work was made possible by the cooperation of Sister Mary Catherine Teresa and members of her staff at the St. Francis Orphan Asylum, New Haven. Dr. Joseph D'Amico of New Haven also assisted.

and they were kept in the infirmary about a week. The jaundiced patients were kept in the infirmary for two to three weeks.

There were no seriously sick patients in this outbreak. Complications were infrequent and occurred only in the icteric patients, consisting of atypical pneumonia in 1 child and generalized acute dermatitis in 2 children. One child had a relapse two and one-half weeks after discharge from his first admission to the infirmary.

Both icteric and nonicteric cases were well scattered through all the juvenile age groups represented at the institution, with no particular concentration among boys or girls. Only 1 adult contracted the disease. The institutional outbreak was coincidental with an increase in prevalence of hepatitis in the local urban population of New Haven as well as in other areas in the state of Connecticut. This was also largely a juvenile disease, for of the cases reported to the Health Department of the City of New Haven (exclusive of those at the asylum described in this paper) about 90 per cent were in children between the ages of 2 and 17 years;³ and of the cases reported during the same period from the practice of physicians in an up state community, this same juvenile prevalence accounted for about 70 per cent of the cases.⁴

The outbreak at the institution was well under way in mid-January, when the decision to test the prophylactic value of gamma globulin was first considered. For this purpose the institution's population was divided on January 27 into four groups (table 1). Primarily, 47 children (group C) who already had had hepatitis or an illness suggestive of hepatitis were eliminated from the experiment as possible immunes. Six of these children in the latter category developed a second illness on or after January 27 with jaundice in 3 and symptoms of hepatitis without jaundice in 4. Adults (group D) also were eliminated. Of the remainder, who presumably represented the susceptible population of the institution, every second and every third child was alternately selected from the alphabetical list for inoculation, giving a ratio of about 38 per cent of the susceptibles to be inoculated. They numbered 97 children and are designated as group A. The remaining 155 susceptible children (group B) were kept as uninoculated controls.

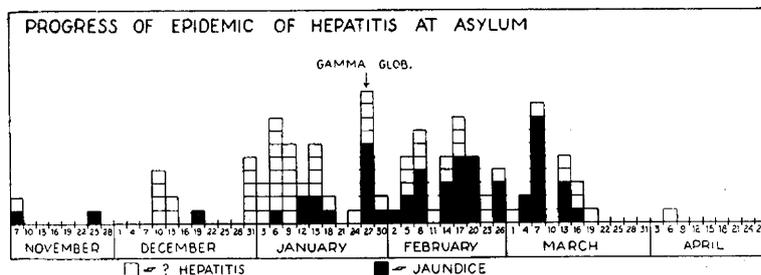


Chart 1.—The outbreak of infectious hepatitis in which gamma globulin was given as a prophylactic measure on January 27.

Gamma globulin⁵ was inoculated intramuscularly on Jan. 27, 1945 into the 97 children in group A. Doses used are listed in table 2. This amount, which ranges from 0.06 to 0.12 cc. per pound, was less by 50 to 75 per cent than that used by Stokes and Neeffe,

3. These figures are for the period of January to May 1945 and were supplied by Dr. Joseph I. Linde, health officer of New Haven.

4. Dr. James J. Derwin, Winsted, Conn., supplied these figures, which cover the period of January to April 1945.

5. The gamma globulin employed in this study was obtained through the Office of the Surgeon General, United States Army. Products of different companies were included, with lot numbers, 3-1 and 3-2, 4-1 and 4-2 for the product of company S; and A 9183 and B 647 for company C.

who employed 0.15 cc. per pound of body weight. No untoward reactions were encountered in the 97 children inoculated.

Rates at which infectious hepatitis developed in the four groups both before and after the inoculation appear in chart 2. In the inoculated children (group A) 2 cases

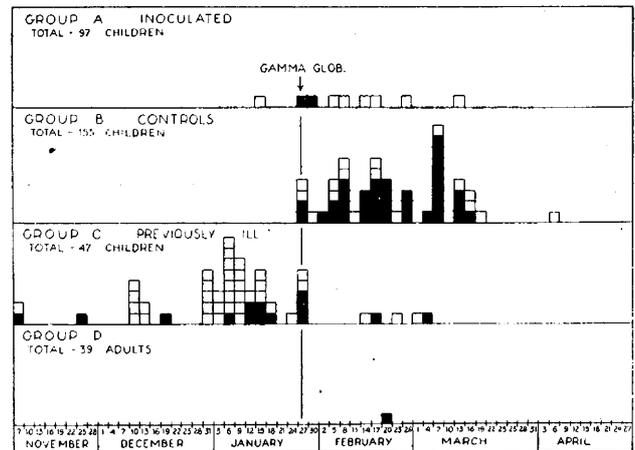


Chart 2.—Rates at which infectious hepatitis developed in four groups of children during an epidemic of hepatitis at an asylum. The open squares indicate cases without jaundice. The black squares indicate cases with jaundice.

of hepatitis with jaundice occurred within six days of the inoculation, and subsequently there were 6 questionable cases of hepatitis (without jaundice) in this group. A comparison of this result with that in the susceptible (group B) controls appears in the two upper panels of chart 2 and in the results listed in table 3. The reduction of cases with jaundice in the group inoculated with gamma globulin is statistically significant. The data do not furnish evidence either for or against the attenuation of the disease by the inoculation.

COMMENT

These results indicate a sharp difference in rate at which jaundice occurred in a group of children inoculated with gamma globulin during an institutional outbreak of infectious hepatitis as compared with a larger group of uninoculated controls in the same institution.

This result was achieved in an outbreak of the juvenile form of disease, which is the common form of the disease in this country.⁶

There may be a number of different types of infectious hepatitis, which represent members of one large general group, as well as a number of varieties of the related condition known as homologous serum jaundice.⁷ It is impossible to say, therefore, whether all of them would respond to the prophylactic injection of the concentrated immune bodies which are contained in gamma globulin.

Infectious hepatitis is a disease which lends itself rather well to the use of prophylactic injections in view of its long incubation period, averaging presumably about twenty-five days. This allows a period of about seventeen days after exposure in which the administration of antibodies is effective in prevention.

6. Blumer, G.: Infectious Jaundice in the United States, *J. A. M. A.* **81**: 353 (Aug. 4) 1923. Molner, J. G., and Kasper, J. A.: An Outbreak of Jaundice in Detroit, *ibid.* **110**: 2069 (June 18) 1938. Molner, J. G., and Meyer, K. F.: Jaundice in Detroit, *Am. J. Pub. Health* **30**: 509 (May) 1940. Norton, J. A.: Acute Infectious Jaundice, *J. A. M. A.* **113**: 916 (Sept. 2) 1939.

7. Paul, J. R.; Havens, W. P., Jr.; Sabin, A. B., and Philip, C. B.: Transmission Experiments in Serum Jaundice and Infectious Hepatitis, *J. A. M. A.* **128**: 911 (July 28) 1945.

CONCLUSIONS

1. The effectiveness of intramuscular injections of gamma globulin was tested as a prophylactic measure in an institutional outbreak of infectious hepatitis.

2. In this outbreak 53 cases of hepatitis with jaundice and another 56 cases of questionable hepatitis without jaundice occurred in a population of about 300 juveniles.

3. Ninety-seven children were given gamma globulin, and the subsequent case rate of hepatitis with jaundice was compared with that in 155 children who were left as uninoculated controls. The case rate for jaundice in the controls was about ten times that noted among those who were inoculated.

4. The only 2 cases of jaundice which did occur in the inoculated children appeared within six days of the administration of gamma globulin.

5. The average dose in this experiment was approximately 0.08 cc. of gamma globulin per pound of body weight given intramuscularly. It seems to have been as effective as the larger dose of 0.15 cc. per pound used by Stokes and Neefe.

6. No evidence is brought forward in this experiment either for or against the fact that the disease might have been attenuated by the injections.

7. It appears that gamma globulin is an effective prophylactic measure against infectious hepatitis when given in the incubation period, preferably earlier than six days before the onset of symptoms. This last statement is based on the study herein reported and on the original observations of Stokes and Neefe.

ADDENDUM

Since this paper was accepted for publication, another and similar report by Gellis, Stokes and others⁸ has appeared. In it the results of a study carried out among troops in the Mediterranean theater in the fall of 1944 are listed. With a dose of gamma globulin of 10 cc. per man (about half that originally used by Stokes and Neefe) success in preventing infectious hepatitis was achieved.

Clinical Notes, Suggestions and New Instruments

COLCHICINE IN ACUTE MYELOGENOUS LEUKEMIA

W. HARDING KNEEDLER, M.D., PHILADELPHIA

The effect of colchicine in arresting mitosis of both animal and plant cells has long been known. As would be expected, rapidly growing malignant tissue is more susceptible to its effect than normal tissue. Many investigators have reported on the effect of colchicine on tumor tissue in culture and in experimental animals. On the basis of this effect on malignant cells in vitro, Dr. O. H. Perry Pepper suggested colchicine in the case of acute myelogenous leukemia herewith reported. He had tried it in 2 acute cases, in 1 of which it had no apparent effect. In the other there was a complete remission, such as sometimes occurs spontaneously, whereupon the drug was discontinued. When relapse occurred the drug was resumed, but the further course of the disease was as would have been expected without the drug.

Two references to the use of colchicine in leukemia were found in the literature. Bernard¹ gave 1 mg. of the drug by injection into the marrow twice a week in a case of acute myelogenous leukemia for a total of six doses, whereupon the

patient died. There was apparently some modification of the blood picture but not of the course of the disease. In the other case,² of chronic myelogenous leukemia, the drug was administered by mouth without benefit.

In the case reported here, when colchicine was begun the disease was acute and the symptoms were of short duration. The progress of the disease soon became less rapid, then favorable. For some months the patient showed the picture of an aleukemic leukemia (though still with a preponderance of very young forms). After losing 58 pounds (26 Kg.) there was progressive gain in weight and strength before she finally slipped into the terminal state of the disease. Colchicine was continued through the course of the disease, certainly without harmful effect and perhaps with actual though temporary benefit. The spleen was not apparently enlarged until shortly before death and then was only 1 cm. below the costal margin, nor was the white blood cell picture what would have been expected if the disease had changed from the acute to the chronic form.

REPORT OF CASE

Mrs. B. N., aged 55, about Dec. 20, 1943 began to notice irregular fever, malaise, painful swollen gums and submental and cervical adenopathy. She had had a slight tendency to spontaneous subcutaneous hemorrhage all her life (a tendency apparently inherited by her daughter). For six months before the symptoms developed, this tendency was slightly, but increasingly, more evident than before.

Blood counts had been done at various times during the preceding ten years and no abnormal findings noted. The last previous one was eight months before, and this showed white blood cells 3,500, polymorphonuclears 85 per cent, lymphocytes 15 per cent.

Examination a few days after onset showed decidedly swollen, spongy and tender gums, and cervical adenopathy, together with swelling and tenderness of the submental and parotid lymph nodes. The spleen and liver were not enlarged, and the examination was otherwise essentially negative except for several subcutaneous hemorrhages.

On December 27 the blood showed hemoglobin 11.2 Gm., 67.5 per cent, red blood cells 3,960,000, white blood cells 29,000, with 95 per cent myeloblasts and promyelocytes. A diagnosis of acute leukemia was made. (This and all subsequent counts were done by Dr. Thomas A. Cope Jr.) A count on December 30 showed white blood cells 52,700, with 83 per cent myeloblasts and promyelocytes. On Jan. 10, 1945 the hemoglobin had dropped to 8.2 Gm., 49.5 per cent; red blood cells 2,950,000. The white blood cell count had risen to 110,400, with 90 per cent myeloblasts and promyelocytes. The patient was becoming weaker and her gums were bothering her more. Dr. O. H. Perry Pepper was called in consultation at this time. He made a slide and confirmed the diagnosis of acute myelogenous leukemia, noting the almost complete lack of platelets, and suggested that colchicine be given. This drug was given in tablets of 0.5 mg. three times a day until there was some diarrhea, and then after a two day interval twice a day, until death supervened thirteen months later. Any attempt to increase the dosage seemed to be followed by diarrhea, but this dosage was well tolerated.

Following the institution of colchicine therapy on January 11 the white blood cell count rose on Jan. 20, 1944 to 145,000, with 51 per cent myeloblasts and promyelocytes and 29 per cent myelocytes. On February 14 the blood count showed hemoglobin 6.1 Gm., 37 per cent; red blood cells 1,880,000, white blood cells 4,900, myelocytes 10 per cent, stabs 22 per cent, segmented 43 per cent, lymphocytes 25 per cent. The mouth and the lymph nodes were immensely better. The fever was nearly gone, and the patient felt greatly improved, though weak. Two blood transfusions totaling 750 cc. helped to improve the anemia. On March 4 the blood showed hemoglobin 9.9 Gm., 60 per cent; red blood cells 3,660,000, white blood cells 2,400, myelocytes 10 per cent, stabs 6 per cent, unidentified

8. Gellis, S. S.; Stokes, J., Jr.; Brothel, G. M.; Hall, W. M.; Gilmore H. R.; Beyer, E., and Morrissey, R. A.: Use of Human Immune Serum Globulin (Gamma Globulin) *J. A. M. A.* **128**: 1062 (Aug. 11) 1945.

1. Bernard, J.: Leucémie aiguë: Essai de traitement par les injections intramédullaires de colchicine, *Sang* **13**: 434, 1939.

2. Paul, J. T.; Brown, W. O., and Limarzi, L. R.: The Effect of Colchicine on Chronic Myeloid Leukemia, *Am. J. Clin. Path.* **11**: 210, 1941.