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THE USE OF HUMAN IMMUNE SERUM
GLOBULIN (GAMMA GLOBULIN)

IN INFECTIOUS (EPIDEMIC) HEPATITIS
IN THE MEDITERRANEAN THEATER
OF OPERATIONS

II. STUDIES ON TREATMENT IN AN EPIDEMIC
OF INFECTIOUS HEPATITIS

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Because of the long period of convalescence following infectious hepatitis with resulting loss of manpower to the United States Army, the present study was conducted in suitable groups in the Mediterranean Theater of Operations in order to determine whether or not gamma globulin is an effective therapeutic agent in lessening the severity of the disease and in shortening the period of convalescence. Stokes and Neefe,¹ pointing out that globulin is often of value if injected soon after the onset of the initial symptoms of measles,² suggested its trial as a therapeutic measure in early infectious hepatitis.

Through the cooperation of an air force in this theater, patients developing infectious hepatitis were made available for the study. The majority of the patients came from one bombardment group and were diagnosed by the squadron physicians, who had extensive experience with the disease. Patients were chosen for the study as soon as possible after the onset of symptoms and signs suggestive of early, preicteric infectious hepatitis. Typical symptoms consisted of an acute onset of fever, chilliness or chills, headache, nausea, vomiting, anorexia and abdominal pain. Suggestive signs consisted of right upper quadrant tenderness and spasm, often with a palpable and tender liver. If there was any suggestion of scleral icterus, the patient was not included in the series. Alternate patients arriving at each squadron or headquarters dispensary were given 0.3 cc. of gamma globulin per pound of body weight. The average total dose of globulin was 45 cc., half of which was injected into each buttock. The only reaction consisted of pain and tenderness at the site of injection owing to the distention caused by the large dose administered. The pain was much less pronounced if the globulin was injected after the patient had been hospitalized and muscular movement thus limited. However, the globulin was administered as soon as a tentative diagnosis of early, preicteric hepatitis was made. The injected and control patients were

This work was carried out under the direction of the Commission on Measles and Mumps of the Army Epidemiological Board, Preventive Medicine Service, Office of the Surgeon General, U. S. Army.

The gamma globulin used in these studies was obtained from pools of plasma, each pool representing 3,000 to 5,000 individuals, collected by the American Red Cross and fractionated, according to the method of Cohn and his co-workers, by various biologic manufacturers. These pools were obtained originally from groups of individuals in the Eastern and Southern regions of the United States.

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

2. Stokes, J., Jr.; Maris, E. P., and Gellis, S. S.: Use of Concentrated Normal Human Serum for Prevention and Attenuation of Measles, *J. Clin. Investigation* **23**: 531, 1944.

evacuated from the dispensaries as soon as possible by plane to the 26th General Hospital in order to maintain a uniform program of clinical and laboratory follow-up of the group. It was understood that, in the attempt to diagnose hepatitis so early in the course of the disease, errors would be inevitable and patients with diseases other than infectious hepatitis would be included. However, it was felt that such cases would fall equally into the injected and control groups and could subsequently be discarded.

A total of 278 patients were admitted to the study; 70 of these developed jaundice subsequent to the time of injection of globulin. The great majority of the remaining patients proved to have hepatitis without jaundice, as indicated by the liver function tests and the subsequent course of the disease.

Before reviewing the hospital course of the injected and control patients, it appeared that the following criteria might be of value in determining whether or not globulin had an attenuating effect on infectious hepatitis once the disease had started: (a) the incidence of jaundice occurring in the injected and control groups, (b) severity and duration of jaundice, (c) length of hospitalization, (d) the duration of the period in which various laboratory tests showed activity of the disease and (e) the frequency of relapse in the two groups.

On the basis of the foregoing criteria the following results were obtained:

(a) *Incidence of Jaundice in Injected and Control Patients.*—Of the 70 patients who developed jaundice subsequent to admission to the study, 31 had received globulin and 39 were control patients. The difference between the two groups is not sufficiently great to be significant.

(b) *Severity and Duration of Jaundice.*—The severity and duration of jaundice proved to be unsatisfactory criteria for judging the attenuating value of globulin, as their variation within each group was so great. Cases with mild and transient jaundice fell equally into the injected and control groups.

(c) *Length of Hospitalization.*—Subjective symptoms determined to a great degree the length of hospitalization necessary in this disease, and since these were appreciably affected by the patient's desire or unwillingness to return to his unit it was impossible to use the period of hospitalization for comparison.

(d) *Length of Time in Which Laboratory Tests Indicated Activity of Disease.*—The only test which was conducted daily for each of the patients and could therefore be accurately compared in the two groups was the methylene blue test.³ The average duration of a positive methylene blue test, counting from the first day of scleral icterus, was ten days for the injected patients and 9.9 days for the controls. Since the cephalin cholesterol flocculation test and the sulfobromophthalein test were not performed at identical intervals for all patients, the time required for these to return to normal could not be accurately determined for the two groups. Therefore the methylene blue test, the only test permitting comparison of the injected and control patients, revealed no evidence in favor of an attenuating effect of globulin.

(e) *Frequency of Relapses.*—Four patients in the control group and 1 in the injected group developed relapse of the disease. Since the total number of

3. Franke, K.: Methylenblau, ein einfaches sehr empfindliches Reagens Zum Nachweis von Bilirubin, *Med. Klin.* **27**: 94, 1931. Gellis, S. S., and Stokes, J., Jr.: The Methylene Blue Test in Infectious Hepatitis, *J. A. M. A.* **128**: 782 (July 14) 1945.

patients with relapse is so small, this difference does not appear to be significant.

It was difficult to compare the cases of hepatitis without jaundice in the treated and control groups. Variation in the severity and duration of this form of the disease was even more evident than in hepatitis with jaundice. No clearcut evidence was obtained indicating an attenuation in the treated group.

COMMENT

In accordance with observations recorded in the majority of virus diseases that homologous immune bodies rarely are effective therapeutically when the symptoms have fully developed, immune bodies also in this epidemic disease appear to have little, if any, therapeutic value. As the present data do not include a large number of cases at their earliest onset, it is still possible that larger amounts of immune bodies in the form of gamma globulin or, more properly, gamma globulin from pools of convalescent plasma may prove effective in therapy. The obvious difficulty in obtaining cases of this disease at their earliest onset is very great and renders the possibility of such a therapeutic approach highly problematic.

The additional possibility that gamma globulin may be of value in the prevention of relapses or recurrences of the disease deserves further investigation.

SUMMARY

A program designed to test the effectiveness of human immune serum globulin (gamma globulin) in the attenuation of infectious hepatitis was conducted in an air force in the Mediterranean Theater of Operations.

Gamma globulin, 0.3 cc. per pound of body weight, was administered intramuscularly to alternate patients presenting the earliest symptoms suggestive of infectious (epidemic) hepatitis.

No evidence was obtained in the patients studied in favor of an attenuating effect of gamma globulin when administered early in the course of the disease.

Clinical Notes, Suggestions and New Instruments

PENICILLIN THERAPY IN PYLEPHLEBITIS

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Pylephlebitis is an inflammation of the portal vein caused by an acute suppurative process in that part of the abdomen drained by the portal vein. The disease carries a high mortality because of the multiple embolic liver abscesses arising from the infected thrombi in the portal system.

The most common condition causing this disease is acute appendicitis; however, gangrenous cholecystitis, infected thrombotic hemorrhoids, diverticulitis or pelvic suppuration may precipitate a portal thrombosis.

The case reported here followed an acute attack of appendicitis, so I shall confine the discussion to this disease.

In 1897 Armstrong¹ reporting in England, stated that this complication caused 5 per cent of the deaths due to appendicitis. Hawkes² in 1938 analyzed a series of 1,463 cases of acute appendicitis in which portal thrombosis occurred but 12 times. This lowered incidence can be attributed to earlier operative intervention in acute appendicitis.

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1. Armstrong, G. E.: Introduction to a Discussion on Appendicitis, Brit. M. J. **2**: 945, 1897.

2. Hawkes, S. L.: Thrombophlebitis of Appendicular Vein, Surg., Gynec. & Obst. **66**: 62, 1938.

PATHOLOGY

According to Crossland³ pylephlebitis usually follows pronounced appendicular disease. Busch and Spivack⁴ reported 4 fatal cases in a series of 635 cases of acute appendicitis. Two of these were gangrenous appendicitis with perforation, and 2 were appendicular abscesses. This fulminating type of appendicitis is usually attributed to the streptococcus. Early in the disease a septic thrombus is found in the terminal branches of the ileocolic vein, and if the thrombus is not removed at time of operation with the appendix the thrombus extends upward or breaks off and lodges in the liver. Early in the disease positive blood culture is rare. Later, when the liver is riddled with abscesses and its venous system is thrombosed, they may be obtained. Empyema of the right chest by direct extension from the liver may occur. Jaundice due to liver destruction is a late finding. Ascites is common and is associated with the massive portal obstruction.

SYMPTOMATOLOGY

In addition to the clinical history suggesting appendicitis, the patient may have a chill. Colp⁵ found a chill in 6.8 per cent of his cases and Kelly and Hurdon in 15 per cent of theirs. Temperature elevations are out of proportion to the amount of appendicular disease. Severe prostration accompanies even the milder cases of thrombophlebitis of the appendicular vein.

TREATMENT

Prophylaxis by early removal of the appendix when inflamed is mandatory. Probably few cases would develop if all cases should come to operation during the first twenty-four hours.

Treatment by ligation of the veins in the ileocolic angle has been most disappointing. Wilms⁶ first suggested this, and his operation was modified by Braun.⁷ Routine ligation of the ileocolic vein is to be condemned, but all should be inspected and ligated if thrombosed.

Sulfanilamide has been used with success in 2 cases as reported by Ottenberg and Berck.⁸

REPORT OF CASE

History.—H. H., a man aged 22, a seaman, admitted June 2, 1944, complained of dull pain in the right groin and a swollen abdomen. The patient had an operation for appendicitis, gangrenous type, done Feb. 10, 1944. This operation was done as an emergency measure at a hospital along the Florida coast. He was transferred to the Marine Hospital in Chicago on June 2, 1944. The history forwarded with the patient stated that on Feb. 10, 1944 the patient presented himself with the typical signs and symptoms of acute appendicitis and was given an immediate operation. The appendix was suppurative with exudate on its outer surface; there were local peritonitis and a turbid peritoneal fluid. Cultures were not made. During the patient's convalescence he developed drainage from the wound, but it healed after about three weeks. On the second post-operative day the patient developed chills and a septic temperature began; that is, he had an afternoon elevation with temperatures running to 101 and 102 F. and chills nearly every day. The white blood cell count was elevated to about 18,000, but the blood cultures were repeatedly negative. The patient had no particular complaints except anorexia and extreme weakness. He perspired freely and subsequently developed an anemia, which was treated with iron and blood transfusions. On April 24 he complained of shortness of breath and fulness of the abdomen; fluid was demonstrated in the right chest. This was subsequently aspirated. The first specimen was slightly turbid and in appearance was serosanguineous. Repeated aspiration a few days later revealed that the specimen was more purulent, was bile stained and had a peculiar odor which is usually associated

3. Crossland, P. M.: Pylephlebitis Complicating Appendicitis, U. S. Nav. M. Bull. **39**: 398, 1941.

4. Busch, I., and Spivack, A. H.: Observations on Acute Appendicitis, Surg., Gynec. & Obst. **70**: 241, 1940.

5. Colp, R.: Treatment of Pylephlebitis of Appendicular Origin, Surg., Gynec. & Obst. **43**: 627, 1926; Chills in Acute Appendicitis, Ann. Surg. **85**: 257, 1927.

6. Wilms: Venenunterbindung bei eitriger Pfortaderthrombose nach Appendicitis, Zentralbl. f. Chir. **36**: 1041, 1909.

7. Braun, H.: Die Unterbindung der Vena ileocolica bei mesenterialer Pyämie nach Appendizitis, Beitr. z. klin. Chir. **86**: 314, 1913.

8. Ottenberg, R., and Berck, M.: Sulfanilamide Therapy for Pylephlebitis and Liver Abscesses, J. A. M. A. **111**: 1374 (Oct. 8) 1938.