Rapid Therapy of Infectious Hepatitis

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INFECTIOUS hepatitis has now risen to fifth place on the New York State Health Department's list of communicable diseases. The prevalence of this disease has been stressed in the daily newspapers, and the national Office of Vital Statistics has said that known cases have tripled in the past three years. A total of 49,722 cases were reported last year, and this probably represents only a fraction of the real total since many physicians do not report their cases. Physicians who have served in the armed forces are particularly alert to the high incidence of this illness and to the difficulties in management with the long morbidity which it entails. The medical press has begun to use the term "the hepatitis problem."

No method for cure of this disease is known. For that matter, Neefe[1] has pointed out in a recent review that there is no proved method of treatment or prevention at the present time. A wide assortment of therapeutic procedures has been advocated, but this in itself indicates the lack of success of any one measure.[2] Heretofore, physicians have been agreed on rest in bed as the most important step in treatment.[1,3,4] This has been reported as the only practical means of placing the liver at rest. Such complete rest in bed usually extends over a period of weeks, and if it is cut too short, a prompt and immediate relapse of the disease may occur. It has also been suggested that rapid ambulation might increase the subsequent incidence of chronic hepatitis and cirrhosis, but this has never been substantiated, and a random sampling of the population as a whole reveals a high level of chronic liver disease unrelated to any preexisting hepatitis.[5]

Treatment by means of a diet is the second important measure now employed. Originally it was felt that a high-carbohydrate, low-fat intake was essential, and then a swing came about with accentuation of a high-protein, high-carbohydrate diet still with low fat. More recently, Leone *et al.*[6] found that patients free

to choose as they pleased recovered faster than those held down by restrictions. The caloric content in itself is important, and a patient must eat well in order to recover from liver disease. Parenteral fluids or feeding cannot attempt to equal the nutritional value and especially the value to the liver of a well-balanced, large amount of food taken and digested by way of the gastrointestinal tract.

Unfortunately, nausea and vomiting are so common in the early stages of hepatitis that adequate nutrition and maintenance of a normal fluid balance may become problems in management. This brings us to a consideration of the use of parenteral fluids, and it can be safely stated that when necessary, enough should be given by vein to protect normal body levels of electrolytes, fluid, and glucose. A popular addition as a supportive measure has been vitamin B_1. Often large amounts of vitamin B complex are included, and from time to time special value has been ascribed to other dietary adjuvants and vitamins such as A and C.[7] Since the introduction of vitamin B_{12} vast quantities of this fraction have been given intramuscularly.[8] No one is really convinced of the value of any of the vitamins as long as a deficiency was not originally present.

For many years crude liver was employed almost routinely because of its supposed favorable effect in cases of cirrhosis. This conclusion has been questioned and crude liver practically abandoned, but the lipotropic substances, such as choline methionine, inositol, and B_{12}, are still used in the hope that some prophylactic measure can be applied to prevent the possibility of fatty infiltration.[9]

With the appearance of the newer antibiotics, hope for specific therapy of infectious hepatitis once more rose. However, no drug has proved curative, and to date the beneficial effect of broad-spectrum antibiotics such as Aureomycin or tetracycline, is uncertain.[10,11] As a matter of fact, minor toxic effects like nausea and vomiting which may be induced by these drugs may further complicate the management of the disease. More important are the reports that Aureomycin can cause further damage to the liver.[12] There is little hesitation, however, in employing broad-spectrum antibiotics in the patient who becomes desperately ill with his hepatitis. If a real state of cholemia develops, the antibiotic may help bring the patient out of coma by sterilizing the gastrointestinal tract and reducing the work load of the liver and may help in preventing a terminal type Bacterium coli septicemia.

Treatment by means of ACTH and cortisone can still be listed as investigational in nature and is under considerable discussion.[13,14] In the panel meeting conducted by Hanger[2] it was pointed out that one group used ACTH routinely for a while in all cases of toxic liver disease. Serial liver biopsies showed rapid disappearance of exudate, and they were impressed by the rapid fall in the bilirubin and the general well-being of the patient. On stopping the drug, however, there seemed to be a prompt relapse, and it was felt that ACTH should be used in selected cases in which the patient fails to improve with other measures, does not eat, and appears quite ill. Other investigators have found that results with ACTH and cortisone are rather spotty and point out such dangers as sudden expansion of the blood volume and hemorrhages.[15,16] Where an acute fulminating course is encountered, however, cortisone may prove a life-saving measure by suddenly reversing the downhill trend.[17,18]

This review of current therapy is intended to outline the varying opinions and impressions of investigators in the field of liver disease and, in mentioning the wide variety of measures employed, to point out once more that no specific treatment is available at this time. Again it should be stressed that the long period of disability and morbidity involved in acute viral hepatitis makes the over-all problem more extensive than is indicated by the high incidence of the disease alone. It was our desire to deal with this problem by developing a more effective method of management or a method of treatment which would bring about rapid recovery in patients afflicted with this illness. To this end we are reporting our results in treating infectious hepatitis with a combination of cortisone and broad-spectrum antibiotics in a definite program.

Methods and Materials

In the past our routine method of treatment of infectious hepatitis was as follows: (1) rest in bed, (2) high-caloric but moderate fat diet with extra feedings, (3) intravenous glucose in saline if the patient complained of anorexia, nausea, or vomiting, and (4) B complex vitamins by injection, multivitamin capsules by mouth,

and occasionally vitamin B_{12} and/or crude liver parenterally.

All the patients were hospitalized (C.R.), and to this program was added the combination of cortisone and a broad-spectrum antibiotic. When the study was first begun, no intravenous cortisone solution was available; later hydrocortisone made its appearance in an alcoholic solution. Ordinary doses of cortisone had been found a complicating factor in treating liver disease, and we felt that small doses given intravenously in drip form might secure better results. Accordingly, one of us (M.J.) prepared a soluble form of cortisone which we continued to use despite the advent of hydrocortisone solution because of the theoretic objection to the alcohol content of the latter.

At first cortisone acetate was merely added to propylene glycol in the proportion of 8 mg. per cc. of the diluent. Later we used a soluble cortisone solution prepared and supplied through the courtesy of the York-Regency Medical Laboratory in New York.

Our cortisone solution was freely miscible in glucose in water, even with the addition of intravenous Aureomycin or tetracycline. Each day an intravenous drip solution was prepared which consisted of 10 to 30 mg. of soluble cortisone and 500 mg. Aureomycin or Achromycin intravenous in 500 cc. of 5 per cent glucose in distilled water. This was administered fairly rapidly in an average time of from one to two hours.

Once the study was started, every case of infectious hepatitis which we encountered in private practice was treated according to standard routine along with the daily intravenous drip therapy of cortisone and antibiotic as described. Twelve successive cases were treated in this way with only minor variations. No patient in whom the diagnosis was made was excluded. Our case histories are given in Table I, and Fig. 1 is a graphic summary of the treatment-time relationship.

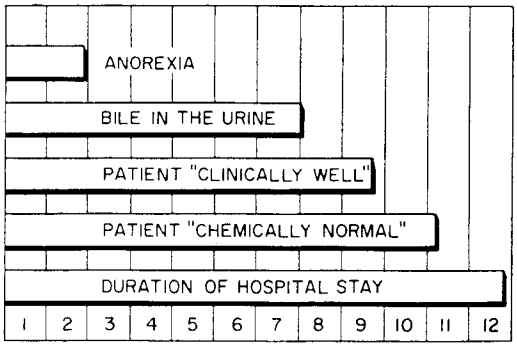

FIG. 1. Treatment-time relationship in 12 successive cases of infectious hepatitis.

Case Reports

CASE 2.—J. P., a twenty-three-year-old, white male museum assistant, had been in good health in the past; this was his first hospital admission. The patient had not been out of New York in the past six months, and there was no history of special medications, injections, or blood transfusions. Two weeks previously he had developed shaking chills and low-grade fever but had continued to eat well and was able to remain at work. Then a week prior to admission he lost his appetite, became nauseated, and began to vomit. The patient admitted to fairly frequent alcoholic excesses and was not too upset by his symptoms until four days earlier when he noted dark urine and was told that he was jaundiced.

Physical examination showed a tall, well-developed young man. The sclerae were icteric, and there was moderate generalized icterus. A slightly tender liver edge was palpable just below the costal margin. There were no other masses, and there was no lymphadenopathy.

Laboratory determinations showed bile in the urine with a urobilinogen of 1:80 and a leukopenia on blood count. Icteric index was 21, bilirubin indirect 2.5 mg., cephalin flocculation 4 plus, and alkaline phosphatase 12.6. The total cholesterol was 185 and esters 112, albumin 4.2, globulin 2.9, and thymol turbidity 8.4. The bromsulfalein retention was 40 per cent and the blood sedimentation rate 21.

Treatment consisted of eight daily intravenous infusions of 10 mg. soluble cortisone and 500 mg. Aureomycin in 500 cc. 5 per cent glucose in water. The patient felt better and began to eat almost at once. Within seven to eight days all clinical and laboratory evidence of jaundice and hepatitis were gone except for the persistence of a rapid sedimentation rate. The patient no longer appeared jaundiced, the urine was free of bile. Icteric index was 6 and cephalin flocculation 2 plus. By the tenth day the patient was ambulatory despite our qualms about a sedimentation rate of 60, cephalin flocculation 3 plus, and thymol turbidity 8.8. He felt well, the liver was not palpable, the urine was free of bile with a urobilinogen of 1:20, and the icteric index was 6, bilirubin 0.2 mg., and bromsulfalein retention only 3 per cent. Incidentally the heterophil agglutination was negative.

The patient was discharged on the twelfth hos-

TABLE I.—SUMMARY OF TREATMENT OF 12 SUCCESSIVE CASES OF INFECTIOUS HEPATITIS

Case	Age	Sex	Onset (Days Before Admission)	Chief Symptoms	Physical Examination	Laboratory Data* — Admission	Laboratory Data* — Discharge	Number of Infusions	Days in Hospital	Recurrence
1	25	M	7	Fever, anorexia, jaundice	Jaundice, liver edge 3 cm. down	Leukopenia, bile in urine, I.I. 26, bilirubin 1.4, ceph. floc. 2+, alk. phos. 23, ESR 19	I.I. 3, bilirubin 0.2, ESR 36, urine clear	7	13	None
2	23	M	14	Chills, fever, nausea, jaundice	Jaundice, tender liver edge	Leukopenia, bile in urine, urobilinogen, I.I. 21, bilirubin 2.5, ceph. floc. 4+, ESR 21, BSP 40%	I.I. 6, bilirubin 0.2, ESR 60, BSP 3%, urine clear	8	12	None
3	40	F	21	Joint pains, anorexia, jaundice	Jaundice, liver edge 3 cm. down	Normochromic anemia, bile in urine, 1:1,280 urobilinogen, I.I. 25, ceph. floc. 2+	I.I. 3, bilirubin 0.8, ESR 25, urine clear	6	9	None[c]
4	23	F	14	Chills, fever, nausea, jaundice, weight loss	Jaundice, tenderness over liver	Slight leukocytosis, bile in urine, I.I. 18, bilirubin 8, ceph. floc. 1+, ESR 19, BSP 37.5%	I.I. 3, bilirubin 0.4, ceph. floc. 3+, ESR 25, urine clear, 1:320 urobilinogen	11	21	None
5	27	M	7	Malaise, nausea, fever, jaundice	Jaundice, tender liver edge	Slight leukocytosis, bile in urine, I.I. 10, bilirubin 2, ceph. floc. 2+, ESR 20	I.I. 8, bilirubin 0.8, ceph. floc. trace, ESR 14, urine clear	7	8	None
6	39	M	10	Chills, fever, nausea	Jaundice	Bile in urine, 1:80 urobilinogen, I.I. 46, bilirubin 11, ceph. floc. 2+, alk. phos. 21, BSP 48%, ESR 35	I.I. 11, bilirubin 2.7, BSP 12%, ESR 25, urine clear	14	15	None
7	24	M	7	Chills, fever, anorexia	Jaundice, tender liver edge 6 cm. down	Lymphocytosis, bile in urine, I.I. 9, bilirubin 6.4, ceph. floc. 4+, ESR 1, BSP 43.5%	I.I. 8, bilirubin 0.97, ceph. floc. 1+, ESR 19, BSP 2.5%, urine clear	10	12	None
8	32	M	9	Headache, chills, fever, weakness, nausea, jaundice	Jaundice, tender liver 3 cm. down	Bile in urine, I.I. 18, bilirubin 2.4, ceph. floc. 2+, alk. phos. 2.7, BSP 20%, normal blood count	I.I. 6.1, bilirubin 0.6, BSP 10%, urine clear	13	13	None
9	25	M	7	Chest pain, anorexia, chills, sweating, jaundice	Jaundice, tender liver edge 3 cm. down	Bile in urine, I.I. 30, bilirubin 2, ceph. floc. 4+, alk. phos. 4, BSP 20%, normal blood count	I.I. 10, ceph. floc. 1+, urine clear	23	18	None
10	32	M	7	Fever, nausea, chills, pain right upper quadrant	Jaundice, pain right upper quadrant, splenic tip palpable	Leukopenia, bile in urine, 1:160 urobilinogen, I.I. 31, bilirubin 4.8, ceph. floc. 2+ to 3+, ESR 70, BSP 33%	I.I. 20, bilirubin 1.8, ceph. floc. 2 + to 3+, urine clear, heterophils negative	14	13	None
11	50	M	1	Chills, fever, anorexia, (had Thorazine)	Jaundice, liver edge 3 cm. down, tip of spleen felt	Slight leukopenia, bile in urine, 1:320 urobilinogen, I.I. 18, bilirubin 3, ceph. floc. 2+, ESR 50, BSP 38.5%	I.I. 3, bilirubin 0.68, ceph. floc. 0, ESR 49, BSP 6%, urine clear	6	8	None
12	28	M	7	Anorexia, fever, pain in eyes, jaundice	Jaundice, liver dullness 3 cm. down	Bile in urine, 1:160 urobilinogen, I.I. 35, bilirubin 7.4, ceph. floc. 3+, alk. phos. 18.5, BSP 22%, normal blood count	I.I. 8.2, ceph. floc. 2+, ESR 6, BSP 7%, urine clear	12	14	None

* Key to abbreviations: I.I., icteric index; ceph. floc., cephalin flocculation; alk. phos., alkaline phosphatase; ESR, erythrocyte sedimentation rate; BSP, bromsulfalein retention.

pital day, and returned to work and drink without untoward result.

CASE 12.—L. S., a twenty-eight-year-old commercial artist, white, single, in good health in the

past, was transferred from another hospital with a diagnosis of infectious hepatitis. His illness began a week ago with fairly sudden onset of poor appetite, malaise, pain in the eyeballs, and fever to 101 F. In two more days dark urine and light stools appeared, and then he noted a yellow color of the eyes. His head ached, there was mild, cramplike abdominal discomfort, and he vomited once.

Physical examination revealed a thin, icteric young man. The general examination was completely negative except for liver dullness percussed 2 to 3 cm. below the costal margin.

On admission the icteric index was 35, direct bilirubin 7.4 and indirect 3.8 mg. The cephalin flocculation was 3 plus, alkaline phosphatase 18.5, and cholesterol 296 with esters 223. The bromsulfalein retention was 22.5 per cent and sedimentation rate 6. Urine showed 4 plus bile and urobilinogen of 1:60 which rose to 1:160 in a later specimen. The blood count was unremarkable.

The patient was treated in the usual manner with the addition of a series of daily intravenous infusions consisting of 500 cc. 5 per cent glucose in water with 500 mg. intravenous tetracycline and 25 mg. soluble cortisone. A total of 12 infusions was given in a period of ten days. In three days the patient began to eat well. On the seventh day the bedside urine specimen was free of bile. In twelve days the icteric index was 8.2, the cephalin flocculation 2 plus, the sedimentation rate still 6, and the bromsulfalein retention 7 per cent. The patient was discharged to his home on the fourteenth hospital day and asked to rest there for a week before returning to his job.

Comment

There is no antiviral treatment of specific nature available against infectious hepatitis, but we believe that we now have a means of management which may produce rapid recovery from this disease. In each case clinical recovery was achieved in about a week, regardless of the original intensity of the disease. Twelve successive cases were treated with the intravenous combination of cortisone and antibiotic as described, and it would be too much to assume that such rapid results could be coincidental since other cases of hepatitis on other services at the same time went through the usual prolonged course.

Certain features of the rapid improvement manifested by our patients are of practical as well as theoretic interest. In all cases except one there was sudden amelioration of toxicity. In twenty-four to forty-eight hours patients felt much better, and there was marked, visible improvement in the general condition. In all cases this included a cessation of nausea and vomiting with subsequent ability to maintain adequate nutrition through normal channels. The high-caloric intake or forced feeding which is of so much importance was at once possible.

A rapid decrease in the amount of bile in the urine took place. As a practical means of following our patients, daily bedside specimens were inspected, and sometimes within a few hours of the start of the therapy there would be an appreciable clearing. The disappearance of bile in the urine usually preceded the point of clinical recovery and provided the signal for repeating the battery of "liver chemistries." In seven to ten days the patients were clinically well, and various indices, such as icteric index, bilirubin, cephalin flocculation, and bromsulfalein retention, were often within normal limits. The blood sedimentation rate proved an exception.

A factor in this rapid recovery was the powerful anti-inflammatory action of cortisone. The objection has been made that in the early stages of the disease, cortisone may interfere with the normal production of antibodies. We feel that in small doses no such undesirable action takes place. As a matter of fact, when given early enough, the anti-inflammatory action may prevent or cut short the so-called obstructive phase of jaundice seen so commonly in hepatitis. This was demonstrated in Case 11 and in Case 5, a young man who was under treatment quite early because his wife had had the infection first, so that he was alert to the symptoms.

Patterson, Dingman, Schwachman, and Thorn[19] have described the choleretic action of cortisone. This may explain the decrease in serum bilirubin levels, but we still believe that the primary beneficial effect lies in decreasing the edema and inflammation found in the diseased liver. The halt in the obstructive phase may follow the decrease in edema about the smaller bile canaliculi. We do not know whether the antibiotic has any direct effect here unless one were to postulate the presence of secondary infection. In any event partial sterilization of the gastrointestinal tract by the antibiotic may be helpful in producing chemical rest for the liver. Finally, with respect to synergistic action between the cortisone and the antibiotic in bringing about a rapid recovery, we can only speculate, but such synergism does seem to exist.

It is important to point out that in none of our

cases was there any evidence of rebound after treatment, nor was there a relapse at any time. At first we were disturbed by our rapid ambulation in the face of blood sedimentation rates which remained elevated. We have no explanation for this phenomenon and can only note that it was seen repeatedly and could persist for three weeks after the patient left the hospital. Although not included in this report, one of us (M.J.) treated four cases on an ambulatory basis when hospitalization was not feasible. These cases were not so well documented but did well clinically and served to make us less concerned about our decision to ambulate our patients early and return them to work.

We feel that in dealing with a disease of high incidence and long morbidity like infectious hepatitis, the results obtained with this combination of antibiotic and cortisone may indicate some gain in attacking the "hepatitis problem."

Conclusions

1. As the fifth most prevalent reported disease and also as an illness characterized by a long period of morbidity, the importance of infectious hepatitis cannot be minimized.

2. The current status of treatment is reviewed with attention to the uncertain approach to specific therapy at present. Reported results with ACTH, cortisone, or antibiotics are spotty.

3. To the usual method of management we added the routine use of a daily intravenous infusion of rather small doses of a combination of soluble cortisone and a broad-spectrum antibiotic.

4. Twelve successive cases treated in this way recovered rapidly. Within seven to ten days all patients were clinically well. The average hospital stay was less than two weeks. There were no complications and no recurrences.

5. The rationale of this form of therapy is discussed.

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