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Aureomycin, Chloromycetin and Terramycin in Treatment of Acute Viral Hepatitis.* (19370)

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(Introduced by J. L. Melnick.)

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The reports of the effectiveness of aureomycin, chloromycetin and terramycin against rickettsial and presumably viral diseases suggested a trial of these antibiotics in the management of acute viral hepatitis. The following is a report of the investigation of the use of these drugs in treatment of viral hepatitis at the Hepatitis Center, 98th General Hospital, U. S. Zone of Occupation, Germany.†

Materials and methods. Subjects. The patients studied in this investigation were male enlisted personnel of the United States Army of Occupation in Germany who were admitted to the 98th General Hospital within the first 10 days of viral hepatitis. It is quite probable that many of these cases were examples of homologous serum hepatitis but, in view of the fact that there are no means at present for differentiating infectious hepatitis from serum hepatitis clinically, the cases have all been classified as viral hepatitis. The diagnosis was made on the basis of characteristic symptoms and signs accompanied by consistent deflection of appropriate tests of hepatic function. All of the patients studied were jaundiced at the time of admission and the subsequent course of disease was mild or moderately severe. Twenty-four patients received 1.0 g of aureomycin orally every 6

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hours for 10 days.‡ Four additional patients received the same dosage orally and 100 mg of aureomycin intravenously every 6 hours for 10 days. Ten patients received orally 50 mg of chloromycetin per kilo of body weight initially and 500 mg every 6 hours for the subsequent 10 days. Terramycin was given orally to 20 patients—1.25 g every 6 hours for 10 days.§ Fifty-four control patients, chosen alternately at admission, received an appropriate placebo by mouth every 6 hours for 10 days. *Management of patients.* The patients were examined daily and observations concerning pertinent symptoms and signs of disease were made. The weight was measured each week. The following tests of hepatic function were made at admission to the hospital and twice a week throughout the period of hospitalization: serum bilirubin (1′ direct and total); cephalin- cholesterol flocculation; thymol turbidity test; γ globulin turbidity test. After the 1′ direct serum bilirubin measured 0.4 mg % the retention of intravenously administered bromsulphalein in the blood was measured each week until 2 determinations of 6.0% or less were obtained. Except for the administration of antibiotics, both treated and control groups were treated in the same way. The diet contained 4200 calories, consisting of 190 g protein, 607 g of carbohydrate and 114 g of fat, supplemented with vitamins and brewer's yeast. Intravenous infusions of glucose were given as required. All patients were kept in bed, with the privilege of going to the bathroom, until all symptoms and signs of hepatitis had disappeared and the retention of bromsulphalein in the blood measured 6.0% or less. They were then allowed to be ambulatory for one week and if there was no evidence of relapse, either clinically or as determined by tests of hepatic function, they were discharged from the hospital either to duty or to a convalescent center.

Results. Clinical observations. There was no significant difference in the incidence or duration of complaints or physical signs of disease in the patients who received antibiotics and the control subjects. Hepatomegaly, anorexia, nausea, hepatic tenderness were the most common findings. The absence of fever and the limitation of abdominal pain in the majority of patients to the first week of disease precluded the possibility of observing the effect of the antibiotics on these points.

Laboratory observations. In general, the patients who received aureomycin had a slightly longer duration of abnormal results in the various tests of hepatic function (Table I). Serum bilirubin, cephalin-cholesterol flocculation and retention of bromsulphalein became normal somewhat earlier in the untreated patients. The same was true of the chloromycetin treated group except for the retention of bromsulphalein which became normal a few days earlier in the patients receiving the antibiotic (Table II). The difference was, however, not significant. Laboratory tests of hepatic function in patients receiving terramycin returned to normal earlier than in the untreated group (Table III). The difference in the two groups is particularly noticed when comparing the time required for the serum bilirubin and bromsulphalein dye retention tests to become normal. In analyzing the mean differences between the treated and untreated patients in relation to these 2 tests the t value in both instances is found to be greater than 2.0. Comparison of the means for the serum bilirubin test indicates a t value of 2.2 and for the bromsulphalein test the value is 2.3. The probability therefore that these means differ by chance alone is less than 5%. In examining the records of these patients it appeared that 4 *terramycin control* patients exhibited a maximum serum bilirubin concentration above 15 mg % while among the terramycin treated patients only one patient demonstrated such a high level. If the serum bilirubin concentration indicates the severity of disease, then the control patients may have been more seriously afflicted. Therefore a reanalysis was done after excluding the values of the 5 patients exhibiting such a high bilirubin concentration. The mean differences between the two groups still remained significant at less than the 5%

‡ Aureomycin was generously supplied by the Lederle Co.

§ The terramycin was generously supplied by the Charles Pfizer Co. The assistance of Dr. Gladys Hobby of that Company is gratefully acknowledged.

TABLE I. Comparison of Course of Liver Function Tests in 24 Patients Treated with Oral Aureomycin and in 24 Control Patients.

	Aureomycin treated						Control group					
		Days after start of therapy when values became normal						Days after start of therapy when values became normal				
Liver function tests	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt
Total serum bilirubin	24	29.1	23.1	4.7	0	0	24	24.2	17.3	3.5	0	0
Bromsulphalein dye retention	24	42.7	28.2	5.7	0	0	22	36.1	14.5	3	0	2
Cephalin cholesterol flocculation	16	23.9	23.3	5.8	5	3	19	19	12.7	2.9	4	1
Thymol turbidity pH 7.8	18	29.1	21.5	5.1	4	2	14	30.5	12.5	3.4	4	6

A = Patients with abnormal values which became normal during period of observation.
B = " " normal values during entire period of observation.
C = " " abnormal " " " " " "

TABLE II. Comparison of Course of Liver Function Tests in 10 Patients Treated with Chloromycetin and 10 Control Patients.

	Chloromycetin treated						Control group					
		Days after start of therapy when values became normal						Days after start of therapy when values became normal				
Liver function tests	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt
Total serum bilirubin	10	30.1	22.1	7	0	0	9	23.9	14.8	4.9	1	0
Bromsulphalein dye retention	10	38.4	18.1	5.7	0	0	9*	46	21	6.6	0	1
Cephalin cholesterol flocculation	9	24.6	16.3	5.5	1	0	8	22.5	15.8	5.6	0	2
Thymol turbidity pH 7.8	7	25.7	12.8	4.8	1	2	9	23.5	12.5	4.1	0	1

* One patient had BSP value of 6.5% at 87 days after start of placebo and was sent to a convalescent hospital for 3 wk, after which the BSP was 6%.
A = Patients with abnormal values which became normal during period of observation.
B = " " normal values during entire period of observation.
C = " " abnormal " " " " " "

level.

Effect of combined intravenous and oral therapy with aureomycin. Four patients received aureomycin both orally and intravenously. On admission, these patients were mildly icteric, the highest total serum bilirubin being 5.8 mg %. Although the small number of patients makes it difficult to appraise the effect of combined therapy, no remarkable benefit was noted. The courses of disease of these patients did not differ noticeably from those of the patients treated orally with aureomycin or from the control patients.

Untoward effects of antibiotics. The gastrointestinal symptoms associated with the use of these antibiotics were difficult to appraise in this study because of the prominence of such symptoms in viral hepatitis. However, there was apparently some accentuation of anorexia immediately after the ingestion of aureomycin. Two patients who received combined oral and intravenous therapy with aureomycin developed cheilosis and stomatitis 5 and 7 days after beginning treatment. One of these patients had a red papular rash on the trunk at the same time, which disappeared

TABLE III. Comparison of Course of Liver Function Tests in 20 Patients Treated with Terramycin and 20 Control Patients.

	Terramycin treated — Days after start of therapy when values became normal						Control group — Days after start of therapy when values became normal					
Liver function tests	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt	A No. of pt	Mean $\bar{x}$	σ	$\sigma_{\bar{x}}$	B No. of pt	C No. of pt
Total serum bilirubin	20	22.7	16.4	3.7	0	0	20	35.2	19.6	4.4	0	0
Bromsulphalein dye retention	19	44.1	17.6	4	0	1	20	61	27.8	6	0	0
Cephalin cholesterol flocculation	19	21.9	16.6	3.8	1	0	19	28.4	22.7	5.2	0	1
Thymol turbidity pH 7.8	12	27.3	20.7	6	2	6	16	40	21.3	5.3	1	3

A = Patients with abnormal values which became normal during period of observation.
B = " " normal values during entire period of observation.
C = " " abnormal " " " " " "

one day after cessation of treatment. Marked improvement was noted in the stomatitis within a week after discontinuing therapy although the cheilosis continued for a month.

Comment. During the course of the investigation of these antibiotics in the management of viral hepatitis, no immediate or remarkable results were observed. The investigation of aureomycin and chloromycetin revealed minor differences between the treated patients and their respective controls, and statistical analysis of these differences revealed a t value of less than 2; therefore, the differences observed were not statistically significant. A comment is required, however, concerning the apparent difference between the course of the terramycin treated group and that of the terramycin control patients (Table III). In reviewing the treated patients with the control patients in order to determine the comparability of the two groups before treatment was instituted, the average age of the terramycin treated patients was found to be 22.8 years; the day of disease on which treatment was started was 9.04; the mean initial serum bilirubin was 5.23. The control patients were quite similar. The average age was 24.4; the day of disease on which placebo was instituted was 9.06, and the mean initial serum bilirubin was 5.9. In neither group was there a patient who demonstrated confusion, coma, ascites, or edema. As mentioned before, four terramycin control patients showed a maximum serum bilirubin after placebo was started which was over 15 mg %. Only one treated patient had such a high serum bilirubin. After discarding these patients in the analysis, the difference between the two groups still remained significant at less than the 5% level. In reviewing the course of all patients in this study, it can be seen from the tables that the terramycin control patients had a longer course than any other group. However, it should be pointed out that the terramycin study was performed about one year after the investigation of aureomycin and chloromycetin. This renders comparison between the terramycin study and the other antibiotic studies of questionable validity. This study was limited by the clinical material to patients only moderately ill and who had reached the icteric phase of the disease before treatment. It was not possible to evaluate the benefit of aureomycin in hepatic coma(1). Furthermore, in a study of this kind it is obvious that no comment can be made as to the prophylactic value of aureomycin, chloromycetin, or terramycin in this disease. The known presence of serum hepatitis in American troops in Germany(2) makes it probable that both serum hepatitis and infectious hepatitis were under observation in this study.

Summary. The usual course of acute viral hepatitis in young adult men was not significantly changed by the use of aureomycin or chloromycetin. Although terramycin ad-

ministration was associated with a more rapid return to normal of liver function tests than observed in a control group, further investigation would be required to determine the significance of this observation.

1. Farquhar, J. D., Stokes, J., Jr., Whitlock, C. M., Bluemle, L. W., Jr., Gembescia, J. M., *Am. J. Med. Sci.*, 1950, v220, 166.

2. Evans, A. S., PROC. SOC. EXP. BIOL. AND MED., 1950, v75, 809.

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Toxicity of Radioiodine and Radiophosphorus in Rats in Doses Comparable To Those Used Clinically.* (19371)

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The widespread use of radiophosphorus (P^{32}) and radioiodine (I^{131}) in clinical practice emphasizes the need for additional data on the toxicity of these isotopes. Except for the monograph of Bloom(1) and other recent reports(2-11) on the distribution and toxicity of these isotopes little information is available on the toxic effects of these substances in dosages used clinically. These experiments were designed to determine the effects of P^{32} and I^{131} administered in doses comparable to those commonly used therapeutically on the growth and histological appearance of the tissues of young albino rats.

Methods. Male rats of the Sprague-Dawley strain initially weighing approximately 100 g were housed, fed and watered under identical conditions during this study. Three groups consisting of 15 rats each received radioactive phosphorus (P^{32}) in doses of 0.066 microcuries per g (Group I-A), 0.100 μc per g (Group I-B), and 0.166 μc per g (Group I-C). Radioiodine (I^{131}) was administered to 3 similar groups in doses of 0.2 μc per g (Group II-C). Ten rats, receiving similar volumes of distilled water, were used as controls (Group III). These doses are comparable to a dose of radioactive phosphorus in a 70 kg man of 4.6 mc (I-A), 7 mc (I-B), and 11.6 mc (I-C), or of radioiodine of 14 mc (II-A), 42 mc (II-B), and 420 mc (II-C). The isotopes were administered by stomach tube in from 5 to 10 ml of solution in a single dose. All animals were weighed 3 times weekly and red and white blood counts and hemoglobin estimations were made at weekly intervals. Six weeks after the administration of the isotopes the rats were sacrificed by decapitation. Terminal blood counts were taken and the total body weight, the liver, kidney and testicular weight were recorded. Aliquots of these tissues were taken for histologic study.

P^{32} administration. The effects of the administration of P^{32} are indicated in Table I. The average body weights in grams were comparable for both the treated (Group I-A, I-B, I-C) and the control (Group III) animals. Table I indicates that there was a slight decrease in the average weight of the liver, kidney and testes of the treated animals over the controls, but expressed in terms of percentage of total body weight, these, with the exception of the testes, were not statistically different from the control animals.

It was noted that especially after the larger doses (Group I-B, I-C) there was a temporary decrease in the total white count but this had returned to control values within 6 weeks. The effect on the red blood count and hemoglobin was not significantly different in the treated and the control groups. Differential blood counts at the time of autopsy revealed a moderate lymphopenia in the treated animals but no other consistent change. Histologic examination of the kidneys, liver, adrenals, and testes failed to reveal any significant

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