Hematopoietic Depression Induced by Chloromycetin

By ALLAN ERSLEV, M.D.

UNTIL RECENTLY Chloromycetin was administered without much hesitation because numerous clinical reports had stressed its low degree of toxicity. The only toxic complications which were considered significant were mild gastro-intestinal reactions and avitaminotic symptoms presumably caused by elimination of a normal bacterial flora. However, a number of reports have appeared recently which indicate that Chloromycetin may exert a depressive action on the bone marrow in some patients. The danger of this depression has been emphasized by editorials in several medical journals and is now widely known.

The following is an account of 2 cases observed at the New Haven Hospital in which Chloromycetin appeared to be responsible for erythropoietic depression. In both cases bone marrow examinations and reticulocyte counts were carried out before, during and after Chloromycetin administration.

CASE REPORTS

Case 1

R. H., 36-90-83. A 67 year old white salesman was admitted to the New Haven Hospital on March 10, 1952 because of severe prostration and high fever. He had been in good health until three weeks before admission when he developed diarrhea and had chilly sensations with fever up to 103 F. The diarrhea subsided temporarily after administration of paregoric, 4 ml. three times a day, for two days and penicillin, 300,000 units a day, for two days. However, the fever continued and he rapidly became weaker. Ten days before admission he had a new attack of diarrhea with dark red, almost black stools. He was given sulfamerazine, 0.5 Gm. every four hours, and continued this medication for five days, receiving a total of 15 Gm. His condition continued to deteriorate and he was admitted to the hospital in a semi-comatose state. Previous to the present illness he had been in perfect health, had never been hospitalized and not received drug treatment of any kind. There was no history of exposure to bone marrow toxins.

On admission the temperature was 102.5 F. and the pulse 134. The patient was acutely ill and disoriented. Except for pallor and dehydration the physical examination was not remarkable. The red blood cell count was 2 million per cu. mm., hemoglobin was 6.5 Gm. per cent, white blood cell count was 3,800 with 80 per cent segmented neutrophils, 17 per cent lymphocytes and 3 per cent monocytes. Reticulocyte count was 2 per cent. A bone marrow aspiration revealed a hyperplastic marrow with marked normoblastic activity consistent with a diagnosis of chronic blood loss. Liver function tests were abnormal; a direct bilirubin of 1.05 mg. per cent and a total bilirubin of 2.12 mg. per cent, cephalin flocculation test 3 plus after 24 hours and 4 plus after 48 hours, thymol turbidity of 9.6 units, thymol flocculation of 3 plus, alkaline phosphatase of 16.7 Bodansky units, bromsulfalein retention of 22.3 per cent after 45 minutes and urine urobilinogen of 10.8 Erhlich units per 100 ml. Serum albumin was 1.7 Gm. per cent and serum globulin was 4.1 Gm. per cent. Cultures of feces and blood yielded *E. typhosa*.

The patients course is plotted in figure 1. During the first three days he received 3,300 ml. of blood and 2.5 Gm. of aureomycin. When the diagnosis of typhoid fever was estab-

From the Department of Internal Medicine, Yale University School of Medicine, and the University Medical Service, Grace-New Haven Community Hospital, New Haven, Conn.

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lished treatment with Chloromycetin was begun, a total of 85.5 Gm. being given during a twenty-five day period. There was a gratifying symptomatic response, the patient became afebrile, but the fecal cultures continued to yield *E. typhosa*. The liver function tests reverted to normal except for slight bromsulfalein retention and 4 plus cephalin flocculation reaction in 24 hours. Serum proteins were restored to normal. A few days after Chloromycetin was discontinued the patient again became febrile and a second course of the drug was initiated on April 14, 70 Gm. being given in a nineteen day period. On April 18 it was noted that his hemoglobin had dropped to 9 Gm. without evidence of blood loss or blood destruction. Bone marrow aspiration revealed cellular marrow with definite decrease in the number of normoblasts. This decrease was thought to be related to the chronic infection. He was given folic acid 10 mg. daily and a multi-vitamin preparation. On May 1 bone marrow study revealed almost complete cessation of erythropoiesis, less than 1 per cent of the cells being normoblasts, and myeloid maturation arrest at the metamyelocytic stage. The megakaryocytes appeared normal. The peripheral white blood cell count had remained below 5,000 per cu. mm. throughout the entire course, the only significant change observed being decrease in the proportion of segmented neutrophiles from 80 to 50 per cent. There was no bleeding tendency and the platelet count was normal. Chloromycetin therapy

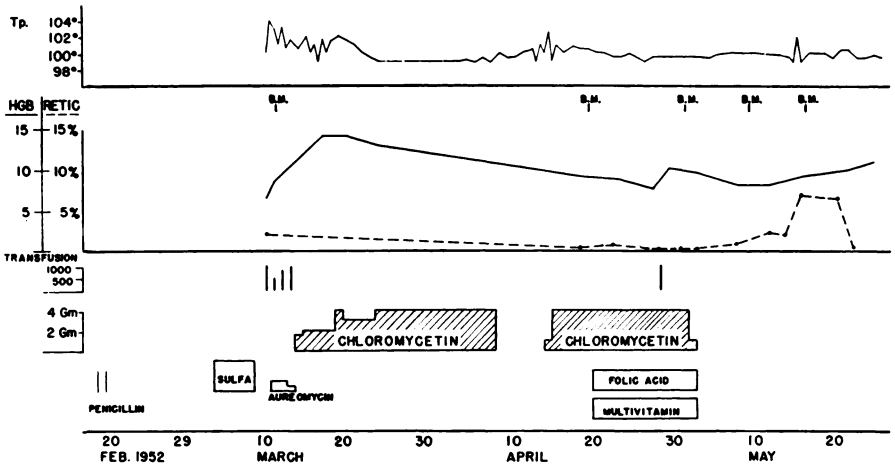

FIG. 1.—Progress chart of Case 1 (R. H.).

was discontinued on May 2. On May 9 re-examination of the bone marrow revealed marked regeneration of erythropoietic tissue and disappearance of myeloid maturation arrest. On May 16 the reticulocyte count reached 6.8 per cent and there was a corresponding rise in erythrocytes. Since then the patient has continued to have positive stool cultures, and on May 29 was discharged as a chronic typhoid carrier.

Case 2

H. B., C61565. A 54 year old, white bartender was admitted to the New Haven Hospital on April 17, 1952 because of shaking chills and fever. He had been in good health until June 1951 when he suddenly developed chills and fever. He was admitted to another hospital and treated with Chloromycetin for three and a half days, penicillin for five days and chloroquine for ten days. At that time a liver biopsy revealed hemochromatosis. From July of 1951 until two weeks before admission he had occasional attacks of shaking chills but felt generally fairly well. Blood counts were checked repeatedly but were normal. During the last weeks before admission he had daily shaking chills with fever up to 105 F. In the past the patient had had a moderate alcoholic intake but he had never been hospitalized or received any kind of drug treatment. There was no known exposure to bone marrow toxins.

On admission the temperature was 98 F., the pulse 86 per minute and the blood pressure 138/70. The patient was in good general condition. His skin had a diffuse grayish-brown pigmentation and there were several spider angiomata on chest and arms. The liver was enlarged almost reaching to the iliac crest. It was smooth, hard and nontender. The spleen was not felt. The red blood cell count was 4.7 millions per cu. mm., hemoglobin was 14 Gm. per cent, white blood cell count 29,400 per cu. mm. with 12 per cent band cells, 71 per cent segmented neutrophils, 13 per cent lymphocytes and 4 per cent monocytes. Platelets were normal and reticulocyte count was 1.5 per cent. Bone marrow aspiration revealed an active marrow with a normal distribution of all cellular elements except for increase in number of mature plasma cells. Liver function tests showed direct bilirubin of 0.58 mg. per cent and total bilirubin of 1.10 mg. per cent, cephalin flocculation test was 1 plus after 24 hours, thymol turbidity was 21.4 units, thymol flocculation was 4 plus, alkaline phosphatase was 12.5 Bodansky units and urine urobilinogen was 1.58 Ehrlich units in 100 ml. Liver biopsy

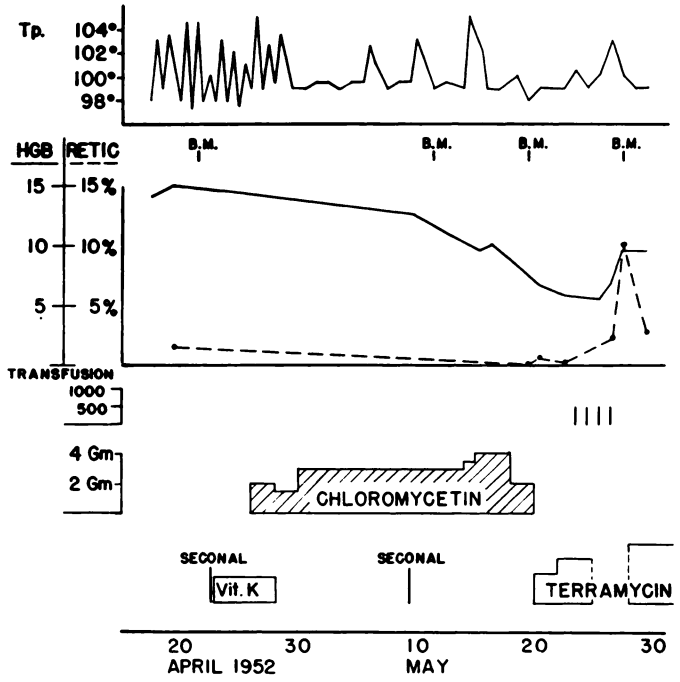

FIG. 2.—Progress chart of Case 2 (H. B.).

revealed hemochromatosis and cholangiolitis. Blood culture and bone marrow culture were positive for *Salmonella montevideo*.

The patient's course is plotted in figure 2. He was given Chloromycetin, and received a total of 66.5 Gm. during the next twenty-four days. Repeated blood and bone marrow cultures were negative but he continued to have occasional chills and fever. On the fourteenth day of therapy his hemoglobin had fallen to 12.5 Gm. per cent but a bone marrow examination two days later showed no significant change. There was no gross evidence of hemolysis, the indirect bilirubin continued to be normal, but the patient had several epistaxes and had numerous red cells in his urine. Bone marrow examination on the twenty-fourth day of therapy showed marked depression of erythropoietic tissue, only 3 per cent of the cells being normoblasts. There was moderate myeloid maturation arrest at the metamyelocytic stage and questionable decrease in the number of megakaryocytes. At that point the hemoglobin had fallen to 7 Gm. per cent and the reticulocyte count to 0.1 per cent. The platelet count was 107,000 per cu. mm. but clot retraction, bleeding time and

capillary fragility were normal. The white blood cell count had decreased from an initial level of 17,000 per cu. mm. to 7000 without significant alterations in differential count.

Terramycin was substituted for chloromycetin and the patient received 2000 ml. of blood. Eight days later the reticulocyte count had risen to 10 per cent and bone marrow study revealed regeneration of erythropoietic tissue with large numbers of normoblasts in nests. Platelet count was unchanged but the white blood cell count rose to 21,000 per cu. mm. The fever subsided slowly during continued administration of terramycin.

Comments

Anemia and hypoplasia of the erythropoietic bone marrow tissue were observed in 2 patients, one treated with a total of 155.5 Gm. of Chloromycetin in fifty days and the other with a total of 66.5 Gm. in twenty-four days. Both patients had received small amounts of other drugs prior to and during Chloromycetin administration. (See figs. 1 and 2.) When Chloromycetin was discontinued a striking reticulocyte response occurred along with reappearance of normoblasts in the bone marrow. This sequence indicates a direct relationship between the administration of Chloromycetin and the observed erythropoietic hypoplasia.

During treatment there was a gradual decrease in the total number of leukocytes, especially the neutrophilic leukocytes, in both patients. The significance of this was not appreciated until a bone marrow examination revealed myeloid maturation arrest at the metamyelocytic stage. Prior to this examination the leukocyte counts had not been regarded as unusual because in the first case leukopenia was looked upon as a manifestation of typhoid fever and in the second case the initial leukocytosis was expected to subside during antimicrobial therapy. It seems significant, however, that when the drug was discontinued the number of circulating leukocytes increased in both cases.

The number of megakaryocytes and platelets was not influenced significantly by therapy. The final hematologic diagnoses were reversible erythropoietic hypoplasia with myeloid maturation arrest induced by Chloromycetin.

Chloromycetin contains a nitro-benzene ring in its structural formula and from the beginning of its clinical use in 1948 it has been considered a potential bone marrow toxin.[1] So far 40 cases have been reported in which administration of Chloromycetin has been followed by maturation arrest or hypoplasia of one or more bone marrow elements.[2-11] Twenty-seven of these cases have terminated fatally.[2, 4, 5, 7-11]

In most of these cases it has been difficult to prove beyond doubt that Chloromycetin was responsible. Idiopathic hypoplastic anemia occurs occasionally and many drugs besides Chloromycetin were administered. However, on the basis of 8 cases (Volini's, Lindau's and the 2 cases reported here) in which discontinuance of Chloromycetin resulted in immediate hematologic recovery, it seems justifiable to assume that the bone marrow depression in all the above mentioned cases probably was caused by Chloromycetin.

The bone marrow changes encountered during Chloromycetin administration have ranged from mild, reversible maturation arrest to severe, irreversible aplasia. Dosage and length of treatment have varied in these cases but most of them had large doses or prolonged treatment.

Bone marrow depression caused by Chloromycetin is still considered a rare

complication. However, when especially looked for, Wilson found it in 2 of 62 treated cases,[4] Lindau in 3 of 8 cases[6] and both cases reported here were discovered within one month. It is possible that hematologic changes observed in infectious diseases treated with Chloromycetin too often have been attributed to the infectious process itself without considering the possibility of drug-induced bone marrow depression.

Knowledge of this complication should result in close hematologic observation of all patients who receive Chloromycetin and immediate discontinuance of the drug if there are any signs of bone marrow depression. It is of importance to follow the red blood cell count and the white blood cell count as well as the blood smear since drug-induced bone marrow depression in its early reversible stage may involve erythropoiesis, myelopoiesis or thrombocytopoiesis independently. Bone marrow examination should be used to check any suspicion of hematopoietic depression. With these precautions it seems safe to continue the use of this valuable antibiotic in cases where it is indicated.

Summary

Two cases of salmonella infection receiving Chloromycetin therapy developed erythropoietic hypoplasia and myeloid maturation arrest. In both cases there was prompt hematologic recovery with well defined reticulocytosis after discontinuance of the drug.

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