All patients had evidence for depression of erythropoiesis coincident with chloramphenicol therapy, in which depression was not judged to be the result of their underlying disease. In one patient (Case 6) a rapidly developing anemia (hematocrit reading 14.5 vol. %) heralded marrow depression. In all patients the reticulocyte counts during toxicity were low, usually below 0.5%. In all 12 available bone marrow aspirations obtained within 48 hours of the last dose of chloramphenicol, there was striking vacuolization of primitive rubriblasts (Fig. 1). Marrows obtained 4 days or longer after cessation of drug therapy did not show these changes. In one instance, vacuolization was observed as early as 6 days after the institution of chloramphenicol therapy. Four days later, another bone marrow smear from this patient showed progression of these changes. No similar abnormalities were observed in control studies of the marrow done after three or more weeks of chloramphenicol therapy in 2 patients who did not develop anemia. Serial marrow observations that were made in 2 patients are illustrated in Figure 2. The course of the erythropoietic depression in these 2 individuals is shown in Figures 3 and 4.

Thrombocytopenia was seen in 4 and leukopenia in one of the patients of this series. Reversal of marrow hypoplasia followed withdrawal of chloramphenicol in the 14 patients who survived more than a few days after the drug was stopped. The rapid marrow recovery which followed cessation of chloramphenicol treatment was usually accompanied by evidence for marrow hyperplasia, such as reticulocytosis and sometimes thrombocytosis and leukocytosis. One patient (Case 1) died of other causes before recovery was complete and another (Case 14) died of unrelated medical causes the day after chloramphenicol was discontinued.

Ten of the patients had mild to severe preexisting liver disease. Three of the four patients selected for serial marrow aspiration had severe alcoholic cirrhosis with hepatomegaly. Although it is known that chloramphenicol is detoxified by conjugation with glucuronic acid in the liver,[5] and that patients with seriously damaged livers may achieve quite high serum levels of free chloramphenicol when treated with 2 gm. a day,[6] we could come to no conclusions regarding the role of these factors in this group of patients.

Four patients in this group had received previous chloramphenicol therapy. Ten received the drug for longer than 2 weeks. In one patient, marrow depression became evident after 71 days of treatment and in another after 40 days. In 8 the drug was given for 2 to 4 weeks. In 5 patients chloramphenicol was administered for less than 2 weeks. Two adult patients received 4 gm. daily (60–77 mg/kg. per day) and four more were given 3 gm. daily (44–90 mg/kg. per day) for a part of the course of therapy which preceded the development of toxicity. The one child in this series received a rather high dose of 2 gm. daily (105 mg/kg. per day). Although 8 patients received no more than 2 gm. daily, every patient in this entire series either received more than 40 mg/kg. per day, or had liver disease.

COMMENT

From the above data, it appears that suppression of erythropoiesis is the most frequent toxic effect of chloramphenicol on the bone marrow. In this series measurable depression of thrombopoiesis and leukopoiesis coincident with treatment with this antibiotic was less common. The frequency with which depression of red cell production by chloramphenicol has been found when sought[2, 3, 3a] strongly suggests that some degree of marrow depression is a common consequence of treatment with this drug. Since the red cell life span is 120 days and the average course of chloramphenicol therapy is 5 to 10 days, brief mild erythropoietic depression easily may be overlooked. In this study the reticulocyte count was found to be the most readily available tool for measuring the effect of chloramphenicol on erythropoiesis. In 12 of the 15 patients that form the substance of this report, the reticulocyte count during drug toxicity was 0.5% or lower. In 2 others, the values represented a significant fall from previous levels. In the remaining case, reticulocyte counts were not done at the height of toxicity.

The bone marrow morphologic changes of chloramphenicol toxicity including reduction in red cell precursors with vacuolization of primitive rubriblasts have been reported by others.[3, 3a, 7] It is likely that vacuolization is a nonspecific change which may result from other causes as well. When these changes are found in a patient who is taking chloramphenicol, until proved otherwise they are indicative of marrow depression by this drug.