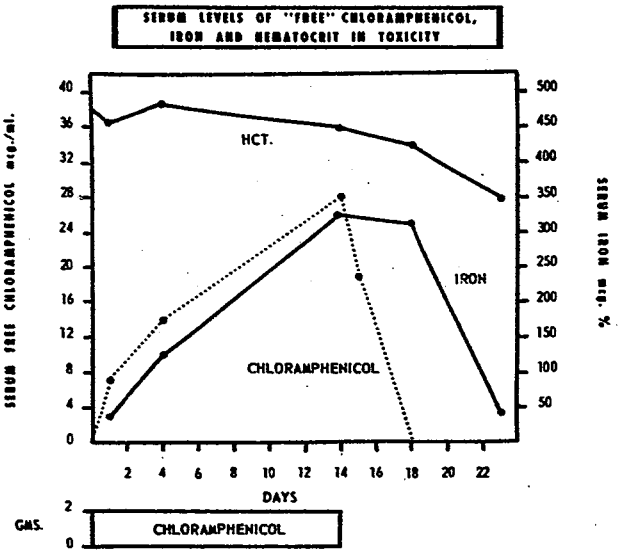

Fig 4.—In a patient with liver disease and toxicity, the relationship between increase in serum iron and free chloramphenicol is demonstrated. The hematocrit did not change significantly until one week after the drug had been discontinued.

COMMENT

The data demonstrate that an increased incidence of erythropoietic depression due to chloramphenicol occurs in patients with hepatic or renal insufficiency. In patients with liver disease the toxicity appears to be correlated with the degree of hepatic damage. Thus, a much higher frequency of toxicity was observed in patients with either jaundice or ascites than in those without these complications. Furthermore, erythropoietic depression occurred in all patients with both jaundice and ascites. No direct correlation was observed between the degree of nitrogen retention and incidence of erythropoietic depression. It should be noted that administration of chloramphenicol was discontinued as soon as a significant rise in serum iron level was observed and before any evidence of erythropoietic depression could be detected in the peripheral blood. Accordingly, one might anticipate a greater degree of toxicity in these patients if administration of chloramphenicol had been continued for a longer period of time. In addition, the amount of drug administered per patient represents a comparatively low dosage schedule. If larger amounts of chloramphenicol had been used, a much higher incidence of toxicity could have been anticipated.

Drug hypersensitivity did not seem to be a factor since previous exposure to the drug had no relationship to the development of toxicity. Furthermore, three patients who had recovered from erythropoietic depression were treated with small daily doses of 250 mg for 28 days. There was no evidence of toxicity in this group.

It is apparent that the toxicity of the free drug and its metabolic products differ. Thus, there was a lack of correlation between arylamine, the monoglucuronide metabolites, and erythropoietic depression. In every instance erythropoietic depression was correlated with a high free chloramphenicol serum level. This suggests that those who developed toxic effects were either unable to conjugate at a normal rate or unable to excrete the free form of the drug.

McCurdy has obtained similar results on the correlation between bone marrow depression and elevated levels of free chloramphenicol in serum or plasma.[8] In this report toxicity was defined by reticulocytopenia and abnormal vacuolated blast cells in the bone marrow. The elevated mean plasma level of free choramphenicol found six-eight hours after a dose of the drug was quite similar to our mean values in spite of different dosage schedules and routes of administration. The metabolites were not measured. It should be emphasized that the blood samples in the present report were drawn 10–12 hours following the last dose of