often given (Table), but in addition, it seems likely from case data that there is an increased susceptibility to this complication in females prior to the menopause. A peak occurrence rate was noted at 6 to 10 years of age by Yunis and Bloomberg and at 3 to 7 years of age in the present series, the differences being in part due to different tabulation intervals. The marked difference between US and non-US reports in this regard suggests that there may be different national medical trends in the approach to use of chloramphenicol. Upper respiratory tract infections are frequent in this age group and account for a high proportion of uses. Thus, one can neither confirm nor refute at this time the possibility that children at this age may be more susceptible to chloramphenicol-induced marrow depression.

Clinical Characterization.—Yunis and Bloomberg interpret the data of their review as indicating that chloramphenicol produces two types of marrow toxicity. They state that the first of these usually occurs during therapy, is associated with a larger total dose, demonstrates a normocellular marrow, shows anemia with or without leukopenia or thrombocytopenia, and is reversible on withdrawal of the drug. The second type shows a delayed onset, is not necessarily dose-related, demonstrates an aplastic marrow with associated pancytopenia, and usually has a fatal outcome. A majority of cases in the current report conform in most respects to the second class, and there is another cluster which fits fairly well into the first class. However, a number of cases fall between or overlap these two groups. For example, nine of 60 patients in the present series who had at least two weeks delay between the last dose and development of the reaction showed a normocellular marrow or one with only isolated cellular depression, whereas Yunis and Bloomberg found no such cases. All combinations of blood cell depression were seen in association with nonaplastic marrows, and half of the current series showing pancytopenia in contrast to a more limited spectrum seen in the series reviewed by Yunis and Bloomberg. Patients with hypoplastic marrows tend to have received a smaller dose of drug, but there is an appreciable overlap. Thus, the 10%, 50%, and 90% intercepts of a cumulative dosage curve for 48 current cases with marrow hypoplasia were 5, 20, and 54 mg per kilogram per day, respectively; whereas for 28 cases with lesser degrees of marrow involvement the corresponding figures were 16, 31, and 88 mg per kilogram per day. These doses are well within usual recommendations. Curves for the duration of therapy were very similar for the two degrees of marrow involvement with a median of 11 to 12 days. The cases reviewed by Yunis and Bloomberg on the other hand, show a median duration of therapy of about 35 days for patients with hypoplastic marrows, and about 20 days for those with nonhypoplastic marrows. Unidentified biases in the reporting of cases may account for this difference between the two series.

The implication of these authors in dividing chloramphenicol-associated blood dyscrasias into two groups is that there may be two separate mechanisms involved. The current study would indicate that the cases as they occur are not always so sharply divisible, and that the possibility of a single pathogenic mechanism is by no means ruled out. Findings in the identical twins reported here would speak for a single mechanism, for the patient with the greater number of prior courses developed typical aplasia, whereas his twin showed a readily reversible, isolated cytopenia.

Preventive Aspects.—The best educated guess as to frequency of this complication, probably an underestimate of true occurrence, is that of Leikin et al.[9] in which it would appear that less than one case of serious marrow toxicity occurs for every 100,000 courses of therapy. The data presently available are not appropriate for further speculation in this regard.

This study does, however, present a good deal of quantitative information relative to the types of drug course which have been associated with this complication. Marrow toxicity has been seen after low doses and high doses, chloramphenicol alone and in combination with other drugs, short courses and long courses, continuous therapy and intermittent therapy, and single courses and repeated courses. Most patients have received chloramphenicol in dosage and duration commensurate with best clinical practice. Unfortunately, however, it cannot be stated that indications for use always conformed to optimal standards.

Most experts would consider chloramphenicol the treatment of choice in

[9] Leikin, S. L.; Welch, H.; and Guin, G. H.: Aplastic Anemia Due to Chloramphenicol, *Clin Pro Chil Hosp Wash* 17: 171–181 (July) 1961.