After onset of blood dyscrasia.—The manner in which chloramphenicol was used in the study sample *after* onset of blood dyscrasia was also observed. In view of widespread medical information on the toxicity of chloramphenicol for bone marrow, it is of interest that 24 of the 138 study cases received treatment with chloramphenicol after the onset and diagnosis of blood dyscrasia. Twenty of these cases were in the "aplastic anemia" category, two in the "other blood dyscrasias" category, and two in the "undiagnosed" category. Recurrent life-threatening infections are a major problem in the treatment of aplastic anemia. The severity of the chloramphenicol-treated infections in the study sample is suggested by the fact that eight persons were infected by *Staphylococcus* and seven by *Pseudomonas*. It is clear that the medical basis for treatment of infections following onset of blood dyscrasias differed strikingly from that of infections preceding blood dyscrasias.

Eighteen of the 24 persons had bacteriological identification of the causative microorganism, and also had antibiotic sensitivity tests. In 10 the organism was sensitive to chloramphenicol and to one or more of the other commonly used antibiotics; in three the test results were not in the medical records. In no case was it stated that chloramphenicol was the only drug to which the organism was sensitive.

Half of the 24 patients treated with chloramphenicol during the course of their blood dyscraisia did not receive the drug until the last two weeks of life, several not until the last day of life. In some cases the risk of chloramphenicol to already severely depressed bone marrow was recognized by the physician and was considered to be less hazardous than treatment of the infection with a possibly less effective antibiotic. In those 12 cases treated with the drug only in the last two weeks of life, the prognoisis was grave in all cases. Those persons received it for only one day in 8 cases, for 2–3 days in 3 cases, and for 7 days in one case. Among the persons who received chloramphenicol earlier than 2 weeks before death two persons received three courses, in one case totalling 7 days and in the other 25 days. The person treated most extensively with chloramphenicol after onset of blood dyscrasia received four courses, two of 10 days each, one of 20 days and one of 4 weeks, beginning 22 months before his death. Since all of the study cases terminated fatally regardless of the nature of treatment, it is impossible to assess the effect of chloramphenicol on the course of the blood dyscrasia.

Only 3 of the 24 persons who received chloramphenicol after onset of a blood dyscrasia had also received it in the 6 months preceding onset of the blood dyscrasia. On additional two persons received it about 8 and 12 months before onset of blood dyscrasias.

Estimate of risk of chloramphenicol-associated fatal aplastic anemia

The number of deaths from aplastic anemia associated with chloramphenicol between 1957 and 1960 was estimated in the following way. The number of study cases in the first 3½ years was multiplied by three since a 1-in-3 random sample of all reported deaths were reviewed. Estimated aplastic anemia deaths for this period were 40, corrected for rounding in the sample. Since a 100 per cent sample of deaths was studied in the last half of 1960, the estimated number 4, is actually the sample value for that period. Thus, it is estimated that a total of at least 44 aplastic anemia deaths with recorded exposure to chloramphenicol occurred in the 4-year period 1957–1960. On the basis of sales data provided by the manufacturer and on the assumption that 4 g. of chloramphenicol was an average course of treatment, the number of persons in California receiving chloramphenicol in the study years was also estimated. The ratio of the estimated number of persons with aplastic anemia who had received chloramphencol to the number of persons receiving the drug in California indicates the risk of fatal aplastic anemia among persons treated with chloramphenicol to be 1:60,000. This estimate of risk is believed to be conservative for two reasons.

(1) The number of deaths from aplastic anemia associated with chloramphenicol is probably underestimated due to (a) exclusion of out of hospital deaths from the study; and (b) incompleteness of hospital records on prior drug administration.

(2) The number of persons in the general population receiving the drug is probably overestimated since (a) available sales figures are not restricted to chloramphenicol prescribed by physicians but also include drug use by veterinarians; and (b) the 4 g dosage used in these calculations is lower than the 10 g estimate generally believed to be the actual dosage administered.