diseases such as diabetes, hypertensive cardiovascular disease, obpstructive uropathy, or renal calculi, but none had any detectable liver disease. There were six white males, seven Negro males, four white females, and two Negro females in the group with ages ranging from 36 to 88 and a mean age of 56.

Sixteen patients without renal or hepatic insufficiency were selected to match as nearly as possible the two previous groups insofar as age and sex distribution and degree of anemia. Four patients had hemiplegia, two patients had amputation of the lower extremity secondary to arteriosclerosis obliterans, two patients had osteomyelitis, four had paraplegia due to trauma, two had quadriplegia secondary to compression fracture of cervical vertbra, two patients had brain tumors.

Chloramphenicol was administered orally in divided doses of 0.5 gm four times daily for a period of one month unless evidence of erythropoietic toxicity as previously defined was detected.[2] Before administering the drug, two initial blood samples were obtained on separate days for peripheral blood and iron studies. Thereafter, samples were drawn once weekly during the study period with patients in a fasting state between hours of 8 AM and 9 AM. Routine blood cell counts were performed at weekly intervals. Serum iron, iron-binding globulin (IBG) saturation, and plasma clearance of Fe^{59} (T/2) and its appearance in the erythrocyte were determined by methods previously described.[2,3] External scintillation counting was performed over the liver, spleen, and sacrum after Fe^{59} administration.

Bone marrow examinations were performed on all patients exhibiting toxic effects as determined by ferrokinetic data and on the majority of the patients included in the nontoxic group.

Assay for chloramphenicol and its metabolic products.—Free chloramphenicol and its chief metabolites were measured in the serum and urine of 45 of the 51 patients included in this report by the following modifications of the methods of Glazko et al [6] and Levine and Fischbach.[7]

Arylamine was determined by diazotization of 1.0 ml of an acid filtrate of serum (prepared by addition of three volumes of 4% trichloroacetic acid to one volume of serum) with 2.0 ml of 0.5% N HCl and 0.5 ml of 0.1% sodium nitrite. After five minutes, 0.5 ml of 0.5% ammonium sulfamate was added and allowed to stand for three minutes and coupled with 0.5 ml of 0.1% naphthylethylenediamine hydrochloride. After incubation at 37 C for three hours, the purple color change was read at 555 mμ and compared with standards (100 mg/liter chloramphenicol, treated as for serum) after correction for undiazotized blanks prepared by substituting water for sodium nitrite.

Total nitro compounds were determined by the above procedure after reduction of 1 ml acid filtrate with 1 ml titanous chloride (0.25% in 0.5 N HCl) for two minutes, followed by precipitation of the titanium by 0.5 ml of 1.4 N NaOH. Correction was made for the preformed arylamine measured above. This fraction consists chiefly of free chloramphenicol plus that conjugated as the glucuronide.

Extractable chloramphenicol, hereafter referred to as the "free" form and representing the microbiologically active form of the drug, was measured by applying the above procedure for total nitro compounds to an extract made by diluting 1 ml serum with 2 ml phosphate buffer (0.2 MpH 6.0), treating twice with 10 ml chloroform-ethyl acetate (3:1), backwashing the extracts with 10 ml of the same buffer, evaporation of the extracts on a water bath, and resolution in 1 ml 1% trichloroacetic acid.

Urine was assayed in the same manner as serum after a 20-fold dilution.

Criteria for erythropoietic depression.—Patients were classified as exhibiting either definite erythropoietic depression (toxic) or no significant depression (nontoxic) on the basis of ferrokinetic studies as well as on the basis of changes in the peripheral blood. A significant rise in serum iron, increase in iron-building globulin (IBG) saturation, prolongation of plasma clearance of Fe^{59}, delayed appearance of Fe^{59} in erythrocytes, and decreased marrow uptake of Fe^{59} were considered evidence of erythropoietic depression. The criteria for considering the changes in these parameters significant of toxicity were essentially the same as those described in a previous publication.[2] The ferrokinetic changes were correlated with a decrease in reticulocyte count and a subsequent fall in hemoglobin and hematocrit values. The appearance of vaculoated erythroblasts in the marrow was considered further evidence for toxicity but was not relied upon as the sole criterion.