patients who received chloramphenicol for minor respiratory infections or some other infection for which the indication for chloramphenicol was questionable or absent.

Toxicity

The most common and serious toxic effect associated with chloramphenicol therapy is the development of aplastic anemia. This may occur after the administration of small doses for short periods or may appear only after prolonged therapy. Aplastic anemia is the most important complication of chloramphenicol therapy; it occurs more commonly in association with this antibiotic than with any other drug.[40-42] If the aplastic anemia is detected early, and the antibiotic is discontinued, the bone marrow may recover, but often the disease ends fatally.

Other forms of bone marrow depression may occur with chloramphenicol therapy, such as leukopenia, granulocytopenia, and thrombocytopenia. These are more likely to be associated with large doses or prolonged therapy and are more likely to be reversible if the drug is discontinued. Consequently, all patients requiring chloramphenicol therapy should have frequent blood counts, at least twice weekly in the early weeks of therapy and once weekly later. However, it should be emphasized that, although frequent blood counts can be relied upon to detect early changes in the peripheral blood, pancytopenia of the bone marrow may occur without warning.

Recent reports suggest that many patients receiving chloramphenicol therapy have demonstrated hematopoietic changes which may be unrecognized but reversible. Some patients exhibited a marked delay in uptake of radioactive iron by the red blood cells and others have developed anemia. The earliest demonstrable toxic effects on the hematopoietic system are an increase in plasma iron and in the saturation of iron-binding globulin, reflecting a decrease in the iron uptake of the erythroid tissue.[43-46]

Morphologic changes resulting from chloramphenicol therapy have been described by several investigators.[16, 30 43-47] A depression in the reticulocyte count below 0.5% occurs in the peripheral blood of most patients during the toxic phase, and bone marrow aspirations reveal striking vacuolation in young erythroid cells.[46] These changes are usually reversible and disappear within a few days after the drug is discontinued. In fact, rapid bone marrow recovery is usually accompanied by evidence of hyperplasia (reticulocytosis and sometimes thrombocytosis and leukocytosis). Such a rebound phenomenon is not observed in those patients in whom the bone marrow depression is not reversible. Chloramphenicol seems to act at the proerythroblast level, at which maximum vacuolation is seen, rather than at the stem-cell level. Patients with anemia in whom the marrow is active appear to be particularly sensitive to the marrow-depressing effect of chloramphenicol. Increasing the dosage of chloramphenicol above 40 mg/kg of body weight appears to induce hematopoietic depression.

When chloramphenicol is administered in higher concentrations than those ordinarily used, it depresses leukocyte respiration and inhibits the synthesis of nucleic acid by normal and leukemic bone marrow cells. The exact mechanism of bone marrow suppression remains unexplained. There has been one case of acute myeloblastic leukemia reported after chloramphenicol therapy.[18]

Premature and newborn infants are particularly susceptible to the toxic effects of chloramphenicol and there have been several reports of deaths of newborn infants due to chloramphenicol therapy.[30, 49-51] In most cases, the drug was given within 48 hours after birth and the majority of infants affected were premature by birth weight. They developed a symptom complex called the "gray syndrome." Almost all of them received doses larger than 100 mg/kg of body weight daily. The symptoms appeared after 3 or 4 days of treatment. The first evidence of toxicity was vomiting or regurgitation of feedings, followed by refusal to suck and abdominal distention. Respiratory distress, flaccidity, and an ashen gray color then developed. Deaths occurred in the seriously affected babies 24 to 48 hours after the onset of the first symptoms. In the others the symptoms usually disappeared within 24 to 36 hours after the drug was discontinued. Blood concentrations, which were reported in a few infants, showed progressive accumulation of total nitro compounds to unusually high levels. However, autopsy studies did not reveal the cause of death and no characteristics changes were found.

Further studies, including the reproduction of the "gray syndrome" in animals, have elucidated the pathogenesis of this entity. In the newborn infant the