(29) has pointed out, when a drug induces decreases in the rate of cell turnover and there is a reduction in the number of adult intestinal epithelial cells, absorptive capacity is reduced.

Repeated oral administration of methotrexate slows the rate of absorption of the drug. Methotrexate can also cause malabsorption of other drugs such as phenobarbital and isoniazid (30).

Methotrexate can cause nutrient malabsorption both with short- and long-term dosage. Methotrexate-induced malabsorption has been studied in children under treatment for acute lymphoblastic leukemia. It has been found that the impact of the drug on the absorptive process, as reflected by changes in D-xylose absorption, is related to the spacing of drug treatments such that if the spacing is at 7-day intervals, the effects are greater than if the drug dosage is more widely spaced (31).

It has been demonstrated that certain drugs (e.g., triparanol) and certain dietary deficiencies (e.g., niacin deficiency) that cause marked intestinal mucosal injury, sensitize the mucosa to gluten toxicity. However this effect has not been found in laboratory rats that received methotrexate. We may assume, therefore, that the malabsorption induced by methotrexate in human subjects is not influenced by gluten exposure (32).

IV. SPINDLE POISONS

The foregoing discussion has shown that mitochondrial injury and mitochondrial arrest can each be associated with drug-induced malabsorption. It is important, however, to establish the concept that those drugs that induce the same ultrastructural changes may differ with respect to their effects on absorptive processes. This concept is well illustrated in relation to the spindle poisons. Spindle poisons include the antiinflammatory, anti-gout drug, colchicine; the antifungal agent, griseofulvin; podophyllotoxin and its synthetic analogues; and the vinca alkaloids. These drugs cause interference with the microtubular system within cells which results in destruction of the mitotic spindle. The microtubular system is composed of alpha- and beta-tubulin. Tubulin has a specific receptor for colchicine, podophyllotoxin, and the vinca alkaloids. Whereas colchicine and podophyllotoxin share a binding site, the vinca alkaloids bind to a different site on the tubulin molecule (33,34).

When cells are exposed to vinca alkaloids such as vincristine or vinblastine, there is a dissolution of microtubules and the formation of intracellular crystals which contain the drug bound to tubulin. Exposure of cells undergoing mitosis to either colchicine or the vinca alkaloids results both in the disappearance of the spindle, because of a block in microtubular assembly, and condensation of the chromosomes, which leads to inhibition of mitosis (35-37).

A. Vincristine Toxicity

Vincristine toxicity includes gastrointestinal side effects. Clinical signs include constipation, which may progress to adynamic ileus and intestinal ulceration (38,39). Guinea pigs treated with vincristine intraperitoneally or intravenously, and killed 1 to 5 days later, show a sequence of intestinal changes. On the first day after injection, necrotic cells are seen in the crypts, and mitoses are in metaphase. Over the following days, gross abnormalities occur with severe villus atrophy which resembles that seen in the acute gastrointestinal radiation syndrome. The epithelial cells of the mucosa are flattened, poorly stained, and are vacuolated. Occasionally polynucleated cells are seen. Signs of mucosal recovery begin on the fifth day after injection of the drug. Alterations in the intestinal intramural nerve plexus (Auerbach's plexus) are also seen. These changes develop within 24 hr after drug administration, and partial recovery is evidenced by the fifth day postdrug administration. Hobson et al. (40), who made these observations, concluded that vincristine has a twofold effect on the small intestine. It interferes with normal replicative function of the intestinal mucosal cells so that the mucosal renewal is inhibited, which results in mucosal atrophy. Also, the drug is neurotoxic to the intestine, as it is in other tissues. Guinea pigs that are injected with vincristine exhibit rapid weight loss, but growth resumes within 1 week after injection. Diarrhea is present during the period of weight loss.

Vincristine is administered intravenously. Frequently, it is used in combination with prednisone to treat acute lymphocytic leukemia. It is also used to treat patients with advanced Hodgkin's disease and in the chemotherapy of acute myelogenous leukemia and histiocytic lymphoma. Occasionally, it is used to treat solid tumors. The major toxicity is not to the gut but to the peripheral nervous system. Indeed, neurotoxicity is the dose-limiting side effect (41).

The fact that vincristine treatment is intermittent, rather than continuous, may explain the absence of a clinically important malabsorption syndrome. Further, the neurotoxic effects of vincristine to the gut wall lead to constipation and ileus rather than to a diarrheal state that might cause transient malabsorption.

B. Colchicine Toxicity

Colchicine, which has long been used as the drug of choice in acute gout, is a spindle poison that arrests mitosis in metaphase (42). Effects of colchicine on the gastrointestinal mucosa were described 20 years ago and were subsequently likened to the effects of x-rays (43, 44). Whereas histological changes in the intestinal mucosa follow colchicine administration, changes under light microscopy are variable. Malabsorption, which occurs with higher dosages of colchicine, may not parallel the extent of the histological abnormalities (45).