Calcium homeostasis is so critical to health, that numerous organs participate in the maintenance of calcium balance. Along with the parathyroid gland, the skeleton, the intestine, and the kidney, the liver also performs necessary functions in calcium homeostasis, often through actions on vitamin D. Predictably, therefore, liver disease may be complicated by disorders of calcium balance and bone disease. Such a clinical disorder provides us with opportunities to study the factors which lead to disordered mineral metabolism and bone disease, and may provide insights useful in prevention of bone disease in the non-affected population. Bone disease is most prominent in cholestatic liver disease, such as primary biliary cirrhosis or sclerosing cholangitis in adults, or congenital biliary atresia in infants. In these conditions, there is severe scarring and damage to hepatocytes, along with defective delivery of bile into the intestine. Other forms of liver disease, including alcoholic cirrhosis, may be complicated by bone disease as well.

Osteopenic bone disease may be severe and debilitating in patients with obstructive liver disease, leading to severe pain and spontaneous fractures. The underlying bone lesion is osteoporosis or loss of bone mass, with a variable degree of osteomalacia (1-4). Diminished bone mass, when advanced, may be observed in bone X-rays, but more sensitive techniques of assessing bone mass, dual beam photonabsorptiometry or CT of the spine, will detect osteopenia at an earlier stage (5).

Although the mechanism of osteoporosis in patients with liver disease is not well understood, the presence of osteomalacia has been largely explained by recent advances in our knowledge of vitamin D metabolism.

The liver participates in vitamin D metabolism in three ways: by providing bile salts required for optimal absorption of dietary vitamin D, by performing the first essential hydroxylation of vitamin D in the process of formation of its active forms, and by controlling the biliary excretion and enterohepatic cycling of vitamin D metabolites (6). The synthesis of vitamin D from 7-dehydrocholesterol in the skin, in the presence of ultraviolet light is, in most cases, insufficient to meet total vitamin D needs. Therefore, a requirement for dietary intake and absorption of the vitamin exists. Absorption of vitamin D requires bile salts, an intact intestinal epithelium, and an intact lymphatic system. Thus, the first and probably most important effect of cholestatic liver disease is vitamin D malabsorption, due to bile salt deficiency in the intestinal lumen. After absorption, vitamin D undergoes hydroxylation by hepatic microsomal vitamin D 25-hydroxylase. It is 25-OH vitamin D which is the major circulating metabolite (one which we can measure as the best index of vitamin D status) and the substrate for the 1-hydroxylase in the kidney. Advanced hepatocellular damage, therefore, may impair this obligatory first step in the activation of vitamin D. The liver also metabolizes vitamin D and 25-OH vitamin D to more polar compounds, including glucuronides, which are excreted into the bile and lost into the feces. Drugs such as phenobarbital, which modify hepatic metabolism and biliary excretion of vitamin D, may increase the risk of osteomalacia.

A survey of serum 25-OH vitamin D levels in patients with liver disease shows that the lowest values are associated with primary biliary cirrhosis (7). Deficiency, as measured by 25-OH vitamin D levels, correlates functionally with impaired calcium absorption, assessed by arm counting after an oral dose of 47 calcium (Fig. 1). Normalization of 25-OH vitamin D levels to greater than 20 ng/ml corrects calcium absorption (8).

Recent studies have demonstrated the supe-
Fig. 1. Percent fractional calcium absorption as a function of serum 25-OH vitamin D. The relationship approximates an hyperbola, suggesting the presence of a saturable mechanism. Normal calcium absorption = 30-50%. From the data of Bengoa, J. et al. (1984): Hepatology, 4, 261-265, and Gerhardt, A., unpublished data.

Priority of 25-OH vitamin D over the non-hydroxylated forms in normalizing serum levels. Not only does the 25-hydroxy derivative bypass the hydroxylation step in the liver, but the 25-OH vitamin D is far better absorbed than is vitamin D, particularly in patients with defective bile salt secretion (9).

Although we can correct vitamin D deficiency, normalize 25-OH vitamin levels, correct calcium malabsorption, and reverse the osteomalacia on bone biopsy, it is disappointing that osteoporosis has not been reversed by these treatments (1, 2, 4). Various approaches, including use of fluoride, are under study, but there is general agreement that the best hope lies in prevention of bone loss, since reversal of osteoporosis is so difficult.

In our laboratory, a recent observation on enhancement of calcium absorption may provide more hope for improving calcium balance in patients at risk (10). We have found that administration of calcium with a corn-derived glucose polymer enhances calcium absorption two- to five-fold in normal subjects. This approach to optimizing calcium absorption in selected patients, along with careful maintenance of vitamin D status could retard bone mineral loss in patients with liver disease. Finally, though, adequate prevention awaits a better understanding of the pathogenesis of osteoporosis in liver disease and in the general population.

REFERENCES