ous problem.[1,2,4-6,15,16] Many reports have focused on the possible etiologies of this problem, and cholestasis appears to be implicated.[16,18,19] However, hepatic impairment associated with TPN in neonates and infants is still not clearly understood, especially hepatic impairment with cholestasis, which sometimes can result in hepatic failure.[5,8,9,17,30,31] The reported hepatic impairment with TPN manifests with: (1) only elevation in serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT); (2) elevation of alkaline phosphatase (AlK-P) and leucine aminopeptidase (LAP) with the appearance of jaundice; and (3) a combination of the two. Cases with only elevated SGOT and SGPT are usually transient, yet hepatic impairment may become irreversible in cases with elevation of total bilirubin, AlK-P, and LAP. Thus, it is highly possible that the more immature the body is, the more severe the hepatic impairment may be, and it may progress to liver failure in some patients, particularly in preterm infants.[1,2,4,6,16,17]

The results of our animal experiments suggest that with the higher concentration of L-form crystalline amino acids administrated, there was a higher possibility of liver impairment and this difference could be demonstrated by comparing the histology findings of groups II and III: degeneration of microvilli in the bile canaliculi occurred more markedly in group III since the total amount of L-form crystalline amino acid was higher. The severe degeneration of microfilaments in group III (Fig. 3b) might thus result in more-severe abnormal bile secretion. In normal condition, the microfilaments can clearly be observed in the microvilli as shown in the control group (group I) in Fig. Ib. In contrast, the structures of microfilaments were completely destroyed or degenerated to granular material, part of which even resulted in vacuolization as shown in Fig. 3b.

The current concepts regarding the mechanisms of bile formation and secretion are that: (1) bile formation begins in the canaliculi, and bile is actively secreted by hepatocytes; (2) the hepatocytes secrete organic and inorganic solutes and generate bile flow; and (3) the bile flow may either diffuse directly from the hepatocytes across the bile canalicular membrane or enter via the paracellular pathway across "leaky" tight junctions. The microfilaments are involved in the paracellular pathway of bile secretion[23,25] and under normal circumstances, the contractile microfilaments play a role in maintaining the normal structure and function of the bile canaliculus.[24-26] Experimentally, some drugs such as colchicines and phalloidin can cause an increase in the microfilamentous pericanalicular network, and this structural degeneration induces a significant decrease in bile flow resulting in cholestasis characterized by dilatation of the bile canaliculi and loss of microvilli morphologically.[26-29] Thus, the microfilaments comprise a very important functional apparatus for bile secretion.

Similarly, it could be suggested that excess amounts of L-form amino acids being administrated through TPN therapy might cause the degeneration of microvilli and microfilaments, which would disturb the bile excretion function and result in bile stagnation in the bile canaliculi. Finally, hepatic impairment with cholestasis would occur. We speculate that in group IV whose livers were more immature, there is a higher risk for induced hepatic impairment when the newborn rats receive TPN treatment, since the microvilli are easily destroyed in this period resulting in hepatic impairment with cholestasis and sometimes even leading to hepatic failure.

The mitochondria, one of the organelles, became swollen when the amount of L-form amino acids increased. This can be seen by comparing Fig. 2b (group II) and Fig. 3c (group III) with Fig. 1b (group I, the control group), which show increased swelling when the amount of L-form amino acids was increased. Swelling of the mitochondria may be due either to regurgitation of static bile from the bile canaliculi injuring the hepatocytes or be directly influenced by the L-form amino acids,[30-32] the mechanism for this required further investigation.

Our present experiment clearly shows that when the amount of L-form crystalline amino acids is increased, hepatic impairment with cholestasis may be more easily induced. For this reason, the amount of the L-form crystalline amino acids should be very carefully controlled when total parenteral nutrition is given.