The aim of this article is to review the current experimental knowledge of mutagenesis in Barrett's esophagus (BE) with special emphasis on the effect of bile salts and acid. Human evidence of direct mutagenicity is rare. Only the correlation of increased quantities and a change in the quality of bile salts with the complications of duodenogastric reflux such as BE and esophageal adenocarcinoma as an indirect marker of mutagenicity has been shown in several studies. Further evidence comes from p53 studies demonstrating an increased number of mutated p53 genes in patients with BE, esophageal adenocarcinoma, or both. Most animal and cellular experiments are carried out in a neutral pH environment, not reflecting the true nature of a reflux episode. The few studies using moderate low acid reflux conditions in combination with bile salts demonstrated a combined effect on mutagenicity. Our current knowledge of bile salt mutagenicity is predominantly based on experiments with hepatocytes and colon cancer cell lines. Future studies must be aimed at esophageal cell lines, cultured Barrett's tissue, and esophageal adenocarcinoma cell lines.