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Suppression of aberrant DNA methylation is a novel approach to cancer prevention, but so far the efficacy of the strategy has not been evaluated in cancers associated with chronic inflammation. Gastric cancers (GCs) induced by Helicobacter pylori (HP) infection are known to involve aberrant DNA methylation and are associated with severe chronic inflammation in their early stages. Using the DNA demethylating agent 5-aza-2’-deoxycytidine (5-aza-dC), suppression of aberrant DNA methylation to prevent HP-induced GCs was investigated using a Mongolian gerbil model. The incidence of GCs induced by HP infection and N-methyl-N-nitrosourea (MNU) treatment as well as global DNA methylation levels were significantly decreased in gerbils treated with 5-aza-dC (50–55 weeks) compared to vehicle. Extra-gastric tissues were tested to assess adverse effects of 5-aza-dC, which included testicular atrophy. The cover micrograph shows a magnified view of tissue sections of nonatrophied testes in vehicle-treated gerbils. These results show that 5-aza-dC treatment can prevent HP-induced GCs and suggest that removal of induced DNA methylation and/or suppression of DNA methylation induction can become a target for prevention of chronic inflammation-associated cancers. See article by Niwa and colleagues (beginning on page 263) for more information.