Animal Studies Implicating Fat and Fecal Steroids in Intestinal Cancer

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Abstract

There is epidemiological and experimental evidence that the ingestion of excessive amounts of fat enhances intestinal cancer formation. This may be due to the interaction of luminal steroids with the bacterial flora in the colon, forming carcinogens or promoting agents.

Increased fecal steroids induced by drugs, diet, or by mechanical means enhance intestinal tumor formation in rats given injections of azoxymethane. The effect appears to be promotional rather than initiative. Dietary fiber inhibits carcinogenesis only when the fat content of the diet is not excessive. Apparently, a quantitative relationship exists between these two dietary elements that further studies may define for prevention of cancer in humans.

Hill and his associates were among the first to suggest that the epidemiological correlation between a high-fat, low-residue diet and cancer of the large intestine might be explained by the altered lipid metabolism which results from the ingestion of such a diet. Their studies plus those of Wynder, Weisburger, Reddy and others support the theory that the consequences of the ingestion of excessive amounts of fat, namely, increased concentration of biliary steroids and alterations in the bacterial flora in the colon, interact in some manner to enhance carcinogenesis (13).

In 1963, Laqueur (4) discovered the intestinal carcinogenic effect of cycasin, a natural plant product which he fed to rats. This led to the synthesis of 1,2-dimethylhydrazine, AOM, and methylazoxymethanol, all of which are potent intestinal carcinogens for rodents. The tumors they induce exhibit striking similarities to those in humans, hence, the model is appropriate for the many investigations now being conducted on a wide scale. We are among those using this model to study the relationship of excessive dietary fat and fecal steroids to intestinal tumorigenesis.

Alterations in the steroid content of the large intestine can be made by the administration of certain drugs. Cholestyramine, a nonabsorbable anion exchange resin known to increase fecal bile acids, was fed to rats that were given s.c. injections of AOM (8 mg/kg) once a week (7). The 2% cholestyramine diet caused a significant change in the number and distribution of intestinal tumors. There was an average 13.5 tumors per rat fed cholestyramine, while an average of only 6.8 developed in the control animals. Furthermore, the increase occurred in the distal small intestine and especially in the distal large intestine.

Another drug that alters fecal steroids is candicidin, a polyene macrolide. This agent appears to act by inhibiting the absorption of cholesterol from the intestine; therefore, its effect on fecal steroids differs from that of cholestyramine. In another experiment, rats given injections of AOM were fed either 2% cholestyramine or 0.04% candicidin in their diets (9). The number of tumors increased to the same degree in both groups of animals, but the distribution was different. The cholestyramine-treated rats developed more tumors in the distal large intestine, as in our first experiment, but the candicidin-fed rats had the greatest number of tumors in the distal small intestine. The feces of the cholestyramine-fed animals had more acidic steroids, while the candicidin group had increased amounts of fecal neutral steroids. This suggests that the enhancing effect of acidic and neutral steroids may vary in different segments of the intestinal tract.

The diversion of bile by transplanting the bile duct to the midsection of the small intestine in the rat results in a significant increase in fecal bile steroid concentration (3). When such animals are given injections of AOM, they develop significantly more tumors in the large intestine than do normal animals.

The ingestion of excessive amounts of fat is known to cause alterations in fecal steroid content and in the fecal flora (10, 11). Rats fed a 35% beef fat diet and given injections of AOM developed more intestinal tumors (average, 10.5) than those fed a normal 5% fat diet (average, 5.9). Furthermore, the tumors in the high-fat diet group were larger and more malignant than those in rats on a normal-fat diet. There were no tumors in animals not given injections of carcinogen. The 35% beef fat diet altered the composition of the major bile acids in the feces. After 2 months of treatment with AOM, the rats on the high-fat diet had greater amounts of deoxycholic and 12-ketolithocholic acids in the feces than did the animals on a normal-fat diet.

Many reports have been published suggesting that high concentrations of fecal steroids are not in themselves carcinogenic but rather act at the promotional phase of carcinogenesis (6). We studied the promotional effect of high-fat diet by feeding a 30% beef fat diet to 8 groups of rats for time periods varying from 1 to 21 weeks after 8 weekly injections of AOM (1). Another group was fed the high-fat diet for 8 weeks before the carcinogen and still another was fed the high-fat diet during the administration of the carcinogen. At other times, the rats were fed a 5% fat diet. The high-fat diet increased tumor frequency up to 2-fold when given for at least 4 weeks after, but not during or before, the injections of the carcinogen. The effect of the high-fat diet occurred even after a delay of 10 weeks from the last injection of the carcinogen to the administration of the high-fat diet. These results are similar to the promoting effects of certain substances observed in murine skin cancer.

Burkitt et al. (2) suggested that an increase in dietary fiber had a protective effect on intestinal cancer, and there have been many studies in animals in an attempt to establish the validity of this proposal. Some studies have supported it, while others developed data which tend to dispute it. In 2 separate studies, we fed animals 3 different fibers: alfalfa, bran, or...
cellulose (8). The diet in one study contained 35% beef fat and 10% of one of the 3 fibers; there was no significant difference in tumor frequency between animals fed the fiber and those on the fiber-free diet. On the other hand, when the animals were given a normal-fat diet (about 5%) plus either 20 or 30% of one of the 3 fibers, there was inhibition of tumor formation, especially in the 30% fiber group. In the first experiment, there was no reduction in the concentration of fecal bile acids in the rats fed fiber, but in the second, there was a significant reduction. The animals fed the high-fiber diet, particularly the 30% fiber, passed 2 or 3 times more feces than the control animals. It is conceivable, therefore, that the reduction in carcinogenicity in these animals is due to a dilution of fecal steroids.

When applied to the human situation, conclusions derived from animal studies are purely speculative. However, it is noteworthy that experimental observations regarding the role of diet and excessive fecal steroids in this animal model, as reported by many investigators, tend to support the findings from human cancer studies done by Hill, Wynder, Weisburger, Reddy and others (13). That excessive amounts of steroids in the colon of humans may be a factor in the etiology of cancer is also suggested by 2 recent case reports of patients who developed cancer of the large intestine after long-term cholestyramine therapy. One man died of cancer of the small intestine after taking cholestyramine off and on for 8 years (5). Another man, age 29, developed cancer of the colon 5 years after resection of the terminal ileum for trauma followed by cholestyramine therapy (12). Both the operation and the drug are known to increase fecal steroids. The association in these patients may not be valid, but on the other hand, the possibility exists. In time, more cases may be reported, but the number probably will be small since the drug is not commonly used for long periods and the possible association between the 2 is not widely appreciated.

References

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