

BACTERIA AND THE AETIOLOGY OF HUMAN CANCER. M. J. HILL and D. S. DRASAR. St Mary's Hospital Medical School, London.

There is considerable current interest in the role of the environment in human cancer. One of the most intimate environmental components is our gut bacterial flora, which may be involved in the aetiology of cancer by (a) producing carcinogens, (b) releasing carcinogenic aglycones from inactive conjugates, (c) inactivating carcinogens and (d) modifying the host defence mechanisms.

(a) *Production of carcinogens or co-carcinogens*

Nitrosamines.—The production of N-nitrosamines from secondary amines and nitrate is promoted by enzymes or metabolites from a range of gut bacteria at normal gut pH values (Hawksworth and Hill, *Br. J. Cancer*, 1971, **25**, 520). They may be implicated in the aetiology of gastric cancer (Hill, *J. med. Microbiol.*, 1972, **5**, xiv) following their formation in the urinary bladder from where they are readily absorbed (Hawksworth and Hill, unpublished results).

Steroid metabolites.—A number of steroids are known to be carcinogenic (Bischoff, *Adv. Lipid Res.*, 1969, **7**, 165) and a role for bacterial metabolites of biliary steroids in human colon cancer has been postulated (Hill *et al.*, *Lancet*, 1971, *i*, 95). In a study of the nuclear dehydrogenation of steroids we have, to date, demonstrated the aromatization of rings A and B (Goddard and Hill, unpublished results).

Amino acid metabolites.—Tyrosine is metabolized by gut bacteria to a range of phenols (Bakke, *Scand. J. Gastroenterol.*, 1969, **4**, 603), many of which have been shown to be co-carcinogenic. Similarly, tryptophan is metabolized to a range of products which are then excreted in the urine together with similar products of hepatic metabolism; many of these have been implicated in bladder cancer (Bryan, *Am. J. clin. Nutr.*, 1971, **24**, 841). The synthetic carcinogen ethionine is produced by *Esch. coli* from methionine (Fisher and Mallette, *J. gen. Physiol.*, 1961, **45**, 1).

Dialkyl hydrazines.—These very potent colon carcinogens may be intermediates in the bacterial reduction of diazo dyes.

(b) *Release of carcinogenic aglycones*

The plant glycoside cycasin, which is not carcinogenic to germ-free rats, is hydrolysed

in the gut by bacteria to release the carcinogenic aglycone (Laqueur and Spatz, *Cancer Res.*, 1968, **28**, 2262). Although cycasin may be unique it may also be an example of a class of plant products with carcinogenic aglycones. The gut flora is involved in the entero-hepatic circulation of some polycyclic aromatic hydrocarbons which results in a failure to excrete these compounds at optimum speed (Smith, *Prog. Drug Res.*, 1966, **9**, 300).

(c) *Inactivation of carcinogens*

This has received very little attention, but the range of metabolic activities of the gut flora makes it inevitable that such detoxification takes place.

(d) *Modification of the host defence mechanisms*

The hepatic detoxifying enzymes are affected by many compounds (*e.g.* barbiturates) and it is likely that such compounds may be produced or inactivated by bacterial action. Similarly, the immune defence systems of the gut are determined to some extent by the gut bacteria. Modifications of hepatic or immune defences may explain the reduced sensitivity of germ-free animals to some carcinogens (Roe and Grant, *Int. J. Cancer*, 1970, **6**, 133).

IMMUNOGLOBULINS AND BACTERIA IN THE HUMAN STOMACH.

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About 10% of patients with pernicious anaemia will develop gastric carcinoma. We are studying the stomach in pernicious anaemia in an attempt to define possible factors in the development of this cancer.

The gastric mucosa in pernicious anaemia is abnormal histologically. The normal parietal and chief cell population is replaced by atrophic gastritis and intestinal metaplasia. The metaplastic epithelium is identical to the absorptive epithelium of the small intestine: it has villi and microvilli which contain enzymes necessary for the absorption of fat and carbohydrates (Rubin *et al.*, *Lab. Invest.*, 1967, **16**, 813; Klein, Slesinger and Weser, *Gastroenterology*, 1968, **55**, 61). This mucosa has a much faster turnover rate than normal gastric mucosa, as shown by its mitotic activity and by the appearance of increased amounts of DNA in the gastric lumen (Croft, Pollock and Coghill, *Gut*, 1966, **7**, 333). The

fast turnover may result from damage to the gastric mucosal cells by immunological hypersensitivity reactions. To date, various studies have demonstrated cellular hypersensitivity to gastric antigens and the presence of circulating autoantibodies. In the present paper, studies on gastric immunoglobulin levels and bacteria, and serum gastrin levels will be described.

The gastric juice in pernicious anaemia contains a large amount of immunoglobulin, particularly IgA which is a reflection of the immunological disturbance in the gastric mucosa. Although there are problems in quantitation of these immunoglobulins by radial immunodiffusion and electroimmunodiffusion (Shearman, Parkin and McClelland, Progress Report: The Demonstration and Function of Antibodies in the Gastrointestinal Tract, *Gut*, 1971, 13, 483) it has been shown that the IgA is mainly of the secretory type, indicating that it is derived from plasma cells in the lamina propria rather than from the serum. The quantity of immunoglobulins may reflect the severity of the immunological process.

It has been postulated that the hormone gastrin has a trophic action on the stomach and this action might also increase cellular turnover. We have confirmed the work of others (Korman, Strickland and Hansky, *Br. med. J.*, 1971, *ii*, 16) that most patients with pernicious anaemia have very high plasma

gastrin levels (above 450 pg/ml) because there is no acid secretion to inhibit gastrin production by the antrum. A minority of patients with pernicious anaemia have normal plasma gastrin levels because of the presence of antral gastritis. As yet, we do not know which group of patients is more likely to develop carcinoma.

In recent years there has been speculation on the relationship between gastrointestinal cancer and the bacterial flora of the bowel which is influenced by dietary factors. It has been postulated that the colonic flora might degrade bile acids into carcinogens. We are examining a similar postulate for the production of gastric cancer in pernicious anaemia. In contrast to the normal stomach, very high counts of bacteria are found in the achlorhydric stomach. *In vitro*, these organisms are capable of degrading bile salts and this also occurs *in vivo* in some cases. The process can be demonstrated by the early appearance of $^{14}\text{CO}_2$ in the expired air after the oral administration of ^{14}C labelled glycocholate (Parkin *et al.*, *Lancet*, 1972, *ii*, 777) and by the presence of small amounts of unconjugated bile acids in gastric aspirates. Unconjugated bile acids are noxious to mucosal cells and this may represent a further cause of gastric damage. The instillation of labelled bile acids into the stomach of colonized patients enables the breakdown products to be isolated.