Gut

Leading article

Cigarette smoking and intestinal defences

The effects of cigarette smoking on the upper digestive tract have been recognised for some time and have been the subject of several recent and historical reviews.¹⁻⁴ However, most of these reports have not included any effect of smoking on the intestine. The discovery of a relation between cigarette smoking and inflammatory bowel disease has focussed our interest on the effect of smoking on intestinal mucosal defences. In 1982 Heatley *et al* and Harries *et al* were among the first to show that patients with ulcerative colitis tended to be non-smokers.^{5,6} This finding stimulated a series of epidemiological reports which showed that, on average, only 13% of patients with ulcerative colitis were current smokers. Patients with Crohn's disease, on the other hand, were more often smokers than controls.⁷⁻⁹ This led to the proposal that smoking had a protective effect in ulcerative colitis, but was perhaps causal with regard to Crohn's disease. More recent studies have shown that former smokers are at a greater risk of ulcerative colitis than either those who have never smoked or current smokers,¹⁰ with an average delay from cessation of smoking to onset of disease of approximately five years.¹¹ Despite increasing numbers of epidemiological studies, there have been few attempts to explain these relationships in terms of mucosal defence mechanisms. There is, however, considerable evidence to indicate that smoking can have profound consequences on intestinal physiology.

Mucosal epithelial defences

Most research studies of the effects of smoking and mucosal physiology have focussed on the respiratory tract. One effect of tobacco smoke inhalation is an increase in mucus production, resulting in the familiar smoker's cough. Mucus, now regarded as a complex protective barrier in the intestine, is defective in patients with ulcerative colitis. In vitro studies of colonic mucus production have shown that patients with ulcerative colitis have reduced mucus production compared with controls.¹² Analysis relative to current smoking habits showed that non-smoking patients with ulcerative colitis had significantly lower mucus production than non-smoking controls, but in those patients who did smoke, mucus production was comparable with control levels.¹³ Furthermore, previous smoking habit also influenced colonic mucus production. In normal individuals, mucus production was reduced in current smokers, and more especially in ex-smokers, those at greatest risk of developing ulcerative colitis.¹⁴ This evidence suggests that previous smoking may somehow disrupt the mucus producing capacity of the normal colon.

The epithelium is the second line of defence of the intestinal mucosa beneath the mucus layer. The integrity and effectiveness of this barrier can be assessed by measuring the urinary recovery of orally administered 'probe' molecules. A pilot investigation measuring the six hour recovery of a range of sugar probe molecules found no apparent differences between smokers and non-smokers.¹⁵ A more recent investigation, however, has found that 24 hour recovery of ⁵¹Cr-EDTA was significantly reduced in smokers, suggesting that smoking did reduce the paracellular junctions in the intestinal epithelium.¹⁶

Smoking also seems to influence rectal blood flow. In a recent study, patients with inactive ulcerative colitis had increased rectal blood flow compared with controls. Although smoking habit had no influence, the effect of acute smoking significantly decreased blood flow, a mechanism possibly related to nicotine induced vasoconstriction.¹⁷

Mucosal immune defences

The initiating stimulus at onset of inflammatory bowel disease is unknown, but the chronic inflammatory nature of the disorder suggests an abnormal response of the systemic, or more likely, the mucosal immune systems. Unfortunately, it is still not known whether these abnormalities are of primary or secondary importance in the pathogenesis of the disease.¹⁸ Systemically, smoking has profound effects on cell mediated immunity, increasing the leukocyte count and selectively increasing CD4+ cells, with a significant increase in the CD4+/CD8+ ratio.¹⁹ Heavy smokers also have depressed natural killer cell activity,²⁰ as well as reduced antibody dependent cell mediated cytotoxicity.²¹ In the respiratory tract smoking has the effect of increasing the quantity and secretory capacity of the alveolar macrophages, while in the cervical mucosa the number and activity of antigen presenting Langerhans' cells is reduced.²²

Humoral immune markers are also affected by smoking. Circulating concentrations of immunoglobulins A, G, and M are reduced in smokers,^{23,24} while IgE values are increased.²⁵ In the intestinal mucosa, active inflammatory bowel disease is characterised by increased plasma cells and immunoglobulin values, specifically increases in IgG and IgM, while IgA remains the predominant isotype.²⁶ In a group of healthy controls, salivary IgA concentrations were reduced in smokers, while IgM values were increased.²⁷ Analysis of in vitro colonic immunoglobulin production in inflammatory bowel disease patients and controls showed that smoking decreased IgA but increased IgG, while IgM values increased

in the control group but decreased in patients.²⁸ This suggests that smoking may interfere with the normal humoral immune defences, and perhaps alter mucosal cell mediated defence mechanisms active in the colonic mucosa.

Inflammatory mediation

The chronic inflammatory nature of ulcerative colitis is perpetuated by a series of inflammatory mediators. Notable among these are the eicosanoids. Prostaglandin E₂ (PGE₂) is increased in inflammatory bowel disease, particularly when the disease is in relapse. However, the importance of this finding is undermined by the observation that cyclooxygenase inhibitors often exacerbate the condition. More recent evidence suggests that leukotriene B₄ may be the most important mediator in maintaining the inflammatory nature of the disorder.²⁹ Smoking also influences eicosanoid levels. In the circulation, smoking increases LTB₄ concentrations 60 fold,³⁰ while alveolar macrophages from smokers have reduced capacity to synthesise and release both prostaglandins and leukotrienes, probably by inhibition of phospholipase activity.³¹ In the gut, smoking reduces both luminal and tissue PGE₂ in the gastric mucosa.^{32,33} In vitro production of eicosanoids by colonic tissue from healthy controls is low in cigarette smokers.³⁴ In ulcerative colitis patients and controls, in vitro colonic production of PGE₂ is significantly increased in light smokers (<10 cigarettes/day), but significantly decreased in heavy smokers compared with those who have never smoked.³⁵ These results support the epidemiological finding of Rudra, who showed that patients with ulcerative colitis who resumed smoking after the onset of their disease improved only if they smoked on average at least 20 cigarettes a day.³⁶

One consequence of chronic inflammation and subsequent cellular infiltrate is the excessive generation of free radicals. These short lived but extremely reactive chemical species can cause tissue and macromolecular damage, and have been implicated in a range of intestinal disorders, including inflammatory bowel disease.³⁷ Potent free radical scavengers, including sulphasalazine, reduce the severity of intestinal inflammation.^{38,39} Free radicals are a normal occurrence in cellular metabolism, and the cell has evolved an elaborate system for inhibiting these reactive species. This includes specialist enzymes such as catalase and superoxide dismutase, and small molecular antioxidants, including water soluble ascorbate and lipid soluble tocopherol. A fine balance between free radical and antioxidant is normally maintained, however, excess generation of free radicals can leave the system deficient, with subsequent tissue and macromolecular damage.⁴⁰ Cigarette smoke is a rich source of free radicals,⁴¹ while the polymorphonuclear leukocytes of smokers have a greater capacity for free radical generation.⁴² Conversely, antioxidant defences are reduced in smokers, with reduced serum and leukocyte concentrations of vitamin C, urate, and β -carotene.⁴³⁻⁴⁵ Although there is no direct evidence to implicate such mechanisms in the pathogenesis of inflammatory bowel disease, these may be fruitful areas of future research. Although smoking is unlikely to achieve acceptance in the management of active inflammatory bowel disease, the investigations of its effects on the intestinal mucosa may identify future areas for clinical research not previously considered.

Conclusions

Cigarette smoking influences a variety of factors that may directly or indirectly affect the intestinal defences. These include colonic mucus, intestinal permeability, rectal blood flow, immunoglobulin secretion, prostaglandin production, free radicals, and antioxidant defences. What remains per-

plexing, however, is the difference between ulcerative colitis and Crohn's disease and their responses to cigarette smoking. Perhaps further investigations into the mucosal effects of smoking may help to unravel some of the mysteries underlying these complex diseases.

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