Progress report

Smoking and the gastrointestinal tract

'Tobacco, divine, rare, super-excellent tobacco, which goes far beyond all their panaceas, potable gold, and philosopher's stones, a sovereign remedy to all diseases. But, as it is commonly abused by most men, which take it as tinkers do ale, 'tis a plague, a mischief, a violent purger of goods, lands, health, hellish, devilish, and damned tobacco, the ruin and overthrow of body and soul.' (Anatomy of Melancholy, Robert Burton.)

The ravages of smoking on the respiratory tract are well documented and equally well publicized. Unassailable facts about the response of the gut to smoking are scarcer. Smoking has long been equated with sin, and on this basis clinicians have recommended its cessation to alleviate a multitude of disorders, frequently without a firm scientific basis. Because of the direct contact of inhaled smoke with the respiratory tract, its likely contribution to the cause of pulmonary disorders justifies such empirical prohibition. The necessity to assume that smoking contributes to gastrointestinal disorders is less obvious, though of course some smoke is dissolved and swallowed. The well known tendency of habitual smokers to be regular drinkers of alcohol also1 must lead to reservations about finding smoking 'guilty by statistical association' in surveys of disease.

Experimental work on the effects of smoking is not easy. Smoking is an intermittent, but repetitive process, and its pharmacological effects may be immediate or delayed; demonstrating that a change in some physiological process is caused by smoking poses formidable problems. The dosage required to produce a significant and measurable change is difficult to determine, not least because nicotine has a double effect: it first stimulates and then depresses autonomic ganglia. Disparities between different studies of smoking's effects on the same physiological process may sometimes be explained by dose-variation alone. Further, although the possibility that smokers may have characteristics which predispose them both to acquire the smoking habit and to the risk of certain diseases8 (perhaps from psychological causes9) is not well supported by experimental data, it cannot be dismissed.

This review will examine reported associations between smoking and gastrointestinal disease, and will particularly try to indicate where experimental support for a causative relationship exists.

Malignant Neoplasms

CARCINOMA OF MOUTH AND PHARYNX
Numerous anecdotal accounts exist to support the belief that smoking is a cause of cancer of lip and mouth8 especially when short-stemmed clay pipes are used. Unfortunately most studies group buccal and pharyngeal neoplasms together, and sometimes add oesophageal ones as well. Excess
Smoking and the gastrointestinal tract

Deaths from cancer of the lip, mouth and pharynx in cigarette smokers have been separately identified\(^5,6\) though alcohol is also strongly incriminated\(^7,8\). Probably alcohol and tobacco are independently associated with cancer of the mouth and pharynx\(^9\). The recurrence rate of cancer of the mouth, pharynx, and larynx after 'clinical cure' was \(40\%\) in smokers compared with \(6\%\) in non-smokers\(^10\), though another study found no difference in recurrence rates\(^11\). Oral leukoplakia is known to be pre-malignant and occurs more commonly in smokers.\(^12\) Pipe smoking may be particularly harmful, and a specific lesion known as stomatitis nicotina is often seen in heavy pipe smokers. Factors other than nicotine may be involved: rabbits' gingiva develop leukoplakia when tobacco smoke is blown on to them, but not if tobacco extract or nicotine is applied\(^13\), while vitamin B deficiency makes the mouse ear susceptible to tobacco smoke.\(^14\)

**Oesophageal Carcinoma**

Several studies showed a higher death rate from oesophageal cancer in smokers\(^6,15,16,17\) whether they smoked cigarettes, pipes, or cigars, and an excess of smokers in people dying of carcinoma of oesophagus and mouth.\(^5\) Doll and Hill\(^17\) pointed out that the relationship might not be a direct causal one, as the rise in oesophageal cancer deaths from 1942 to 1962 was only \(8\%\) compared with \(325\%\) for lung cancer.

Other workers found more smokers in patients with oesophageal cancer than in control populations.\(^18,19,20\) The relationship is stronger in males.\(^21,22,23\). Alcohol consumption was also higher in the cancer patients.\(^23\)

A necropsy study of oesophageal epithelial histology showed that smokers had a high incidence of abnormalities, some of which were considered pre-malignant.\(^24\)

It can be concluded that smoking may be an aetiological factor in oesophageal carcinoma, but is not the major cause.

**Gastric Carcinoma**

Most major studies find no increase of deaths due to gastric neoplasms in smokers\(^5,6,15,17,25\) though Dorn's study\(^16\) of 1962 indicated a risk in cigarette smokers of 1.86 times that for non-smokers (compared with 2.18 for cancer of mouth and oesophagus). In Poland an excess of male smokers was found in those dying from gastric carcinoma, predominantly at the cardiac end.\(^22\)

**Colon Carcinoma**

There have been no reports of an increased risk of large bowel cancer in smokers. In fact some studies have reported a lower incidence in smokers, though not of significant degree.\(^15,22\)

**Pancreatic Carcinoma**

While the earlier major studies\(^15,16,17\) showed no significant excess of pancreatic cancer in smokers, Hammond's 1964 study\(^8\) showed that cigarette smokers (not pipe or cigar smokers) had a higher death rate from pancreatic cancer. This was supported by his smaller 'matched pair' analysis. There is no experimental evidence to suggest a causative mechanism and the difficulty of making positive diagnoses of pancreatic carcinoma, save at necropsy,
leads to hesitation about accepting smoking as an important cause of the disease.

**LIVER CANCER**
While several series report an increased incidence of liver cancer in smokers no distinction is drawn between primary and metastatic growths. No worthwhile conclusions can be drawn.

**Peptic Ulcer**
An association between smoking and peptic ulceration (particularly gastric ulcers) has been shown in a number of ways.

**DEATH RATES**
There is an increased death rate from peptic ulcers in smokers. Curiously the mortality was greatest in moderate or light smokers rather than in heavy smokers. Hammond found that the risk of dying from a gastric ulcer was significantly higher in cigar and pipe smokers as well as in cigarette smokers.

**INCIDENCE OF PEPTIC ULCERS IN SMOKERS**
A survey of men over 60 showed peptic ulcer to be commoner in cigarette smokers though not in pipe smokers.

**INCIDENCE OF SMOKING IN PEPTIC ULCER PATIENTS**
The first study, in 1927, showed that 82% of males with peptic ulcer were smokers compared with 72% of a control population—an insignificant difference. Seven years later Trowell found that more patients with duodenal ulcers smoked than did controls, and more of them inhaled the smoke. In patients with acute bleeding from, or perforation of, a peptic ulcer, an increased number of cigarette smokers was found. In patients admitted to the Central Middlesex Hospital for treatment of peptic ulcers there was a significant excess of smokers among the gastric ulcer patients of both sexes, and in male duodenal ulcer patients. Massachusetts physicians with peptic ulcers more often smoke than do their colleagues without ulcers, and those with duodenal ulcers started smoking at an earlier age.

**SMOKING AND ULCER HEALING**
In a study of the effect of an antacid regime on the symptoms of peptic ulcer it was found that non-smokers responded better and had fewer exacerbations than smokers. However, a follow-up study of patients after acute perforation of an ulcer showed no improvement of symptoms in those who stopped smoking, although severe symptoms tended to be associated with smoking—this suggested an indirect relationship.

A careful study of gastric ulcer healing, in which ulcer size was measured radiologically, also showed no alteration in symptoms among those advised to stop smoking. However, the reduction in ulcer size was significantly greater in those advised not to smoke, though the number of ulcers which healed completely was almost identical in the two groups. Moreover patients who never smoked anyway showed no greater healing than smokers not advised to stop.
ANIMAL EXPERIMENTS
Dogs who inhale cigarette smoke through tracheostomies do not develop peptic ulcers, but if they are also given histamine injections they develop ulcers more often than dogs given histamine alone. Rats whose oesophagus is perfused with acid alone sometimes develop duodenal ulcers, but the addition of subcutaneous nicotine considerably increases the risk, though nicotine alone does not cause ulcers. The addition of nicotine also increases the likelihood of duodenal ulcers developing in rats subjected to carbachol-pentagastrin infusions.

CONCLUSION
The evidence that smoking is a major cause of peptic ulcers is insubstantial, though there is no doubt that ulcers are commoner in smokers and contribute to their death more often than in non-smokers. (Indirect effects such as a higher incidence of respiratory disease increasing the mortality from anaesthesia could play a part here.) It also seems likely that continuing smoking inhibits healing of gastric ulcers. It has been suggested that ulcers and smoking have a common cause.

Smoking and Gastric Secretion

IN MAN
In a search for the possible mechanism whereby smoking could cause dyspepsia, attention has predictably focused on gastric secretion. The conclusions are more memorable for their disparity than for any light they cast on the association. Every reported study has used significantly different techniques, itself a reflection on the difficulty of reproducing a physiological situation which can be accurately measured.

An early test meal method showed that in patients with 'functional gastric disturbances' and with duodenal ulcers smoking tended to produce 'hyperacidity'. Basal acid output was not significantly changed after smoking four to seven cigarettes in Schnedorf and Ivy's study, but later work showed an increased output in 40% of control subjects and in 85% of peptic ulcer subjects after one cigarette. Piper and Raine found that four to six cigarettes in an hour increased the volume and acid output of basal secretions. Using an 'alcohol test meal' two cigarettes were found to increase acid concentrations in both normal subjects and those with peptic ulcers. Cooper and Knight used modern techniques to measure acid output basally during smoking and during stimulation with meat broth and insulin in patients with duodenal ulcers. Basal output (volume, pH, acid concentration, and pepsin concentration) was the same in smokers and non-smokers, and subsequent changes were no greater during and after smoking than in controls. Debas and his colleagues used the method of continuous stimulation by pentagastrin to produce 50% of maximal acid output. Three cigarettes smoked in an hour did not affect it. Wilkinson and Johnston also used a submaximal infusion of pentagastrin (though they did not relate the level to the patient's maximal output) and showed that smoking one or two cigarettes caused a fall in acid and pepsin secretion. Intravenous nicotine produced a similar reduction.
No change in volume or constituents of gastric mucus was induced by smoking in one study.45

IN ANIMALS
Interesting and paradoxical effects have been observed. Tobacco smoke condensates and nicotine depress gastric juice volume, acid concentration and output, and peptic activity in rats46, 47, 48 both basally and when treated with maximal or submaximal doses of histamine or pentagastrin. However, administration of nicotine for two weeks stimulates volume, acid, and pepsin output. In cats, an infusion of nicotine at 400 \( \mu \)g/hour decreased a ‘near-maximum’ gastric response to pentagastrin, whereas half that dose of nicotine has no effect. However, if peptic ulcers are produced artificially by pentagastrin infusion the addition of nicotine at the lower dose produces more ulcers, while at the higher rate it causes fewer ulcers.49

In a study on dogs50 it was found that nicotine injections affected neither basal nor half-maximal gastric secretions. However, they inhibited a near-maximal secretion of pancreatic juice (both volume and bicarbonate concentrations) and diminished volume and bicarbonate content of bile. This confirmed the original observations made by Edmunds in 1909.51

CONCLUSION
No clear conclusion can be reached from the confusing data shown above. Perhaps smoking can both increase basal gastric secretory output and diminish stimulated but submaximal output; both effects may be dose-dependent. Certainly no conclusion is possible about the likelihood of smoking causing peptic ulcers or adversely affecting their healing, through the medium of gastric secretory changes.

The unconfirmed studies of pancreatic inhibition by nicotine raise the interesting possibility of diminished duodenal neutralization being the relevant mechanism of smoking’s contribution to peptic ulceration.

Gastritis

In their careful study of histologically demonstrated atrophic gastritis, Edwards and Coghill52 found that, in people over 50, gastritis was much commoner in heavy cigarette smokers. In shorter-term experiments photographs of the gastric mucosa were taken before and during cigarette smoking.53 Four of six subjects showed blanching of the mucosa, though ‘Tom’s’ stomach had not shown any change on smoking in Wolf and Wolff’s famous experiments.54

*Since this review was prepared a study has been published (Bynum, T. E., Solomon, T. E., Johnson, L. R., and Jacobson, E. D., 1972) showing that cigarette smoking inhibited the volume and bicarbonate content of pancreatic juice during smoking in light smokers, while heavy smokers (more than one packet a day) showed a lower output of pancreatic juice than controls even when they were not smoking.

Reference
Gastrointestinal Motility

OESOPHAGUS
Smoking causes a fall in lower oesophageal sphincter pressure, inhaled nicotine probably blocking the cholinergic control mechanisms as it does in vitro. The fall in sphincter pressure is often accompanied by gastro-oesophageal reflux, explaining the higher incidence of symptomatic reflux observed in smokers.

STOMACH
No consistent change in gastric motility has been observed with smoking. Radiological examination has suggested paralysis of peristalsis, increased peristalsis, or no change. Balloons in the stomach detected increased, decreased, and unchanged motility in equal proportions of patients studied by Batterman, though in another study a fundal balloon recorded no change in motility on smoking. Studies of gastric emptying have been technically imperfect.

COLON
Smoking has frequently been observed to produce a call to stool, though the motility change has not been positively identified. In patients with the irritable bowel syndrome smoking may precipitate colonic hypermotility.

COMMENT
The lack of firm data on the effects of smoking on most aspects of gastrointestinal motility is disappointing. It presumably reflects both the difficulties in measuring motility accurately, and the problems of assessing the effect of a mixture of drugs in variable dosage—which smoking effectively is.

Non-malignant Oral Disease

Aphthous ulcers have been observed to be less common in smokers, and even to heal better when smoking was resumed. The deposition of tar on the teeth of smokers is commonly observed. Dental calculus is commoner in smokers, particularly in the supragingival area.

The evidence regarding smoking as a cause of periodontal disease is not uniform. Some workers found a positive relationship while others have not.

Three cases are reported in which cessation of smoking alone led to rapid remission of severe oral moniliasis and acute oral infections such as Vincent's gingivitis are more likely to occur in smokers.

Cirrhosis

Deaths from hepatic cirrhosis are more frequent in cigarette smokers than in non-smokers, but this is probably due to the strong association between heavy drinking and heavy smoking.

JOHN R. BENNETT
Gastro-Intestinal Unit,
Hull Royal Infirmary,
Kingston upon Hull
The Librarians of the Hull Medical Library have painstakingly sought out references, and the librarians of the Tobacco Research Council and British Dental Association kindly helped with the bibliography. Miss A. Evans bore the brunt of the typing.

References

Smoking and the gastrointestinal tract


