Editorials

Smoking and peptic ulceration

Slightly more than 50 years ago Barnett (1927) reviewed retrospectively, from hospital records, the smoking habits of patients with peptic ulcer. From comparison with a control population he concluded that the purported relationship of smoking and peptic ulcer did not exist. Soon afterwards Gray (1929) recorded that cessation of smoking promoted ulcer healing. The many epidemiological studies which followed pointed, with few exceptions, to a connection between smoking and peptic ulcer. The more sophisticated surveys of the past decade have recently been reviewed authoritatively by the US Department of Health, Education and Welfare (1979). Overwhelmingly the evidence confirms the results of the earlier surveys and leads to five conclusions: there is an increased frequency of smoking in both duodenal and gastric ulcer patients when compared with controls; there is an increased prevalence of peptic ulcer (approximately two-fold) among smokers of both sexes when compared with nonsmokers; the incidence of peptic ulcer increases with increasing numbers of cigarettes smoked; cigarette smoking retards the healing of both gastric and duodenal ulcers; and male cigarette smokers have a twofold greater chance of dying from peptic ulcer than male nonsmokers.

If, after 50 years, the clinical facts at last seem reasonably clear, the mechanism by which smoking promotes peptic ulceration has still to be unravelled. Peptic ulcer highlights the general problem of all multifactorial diseases, which is that a number of factors can be shown conclusively to influence a pathological process, but only by a small extent. The task is to discover how such factors can act at a cellular or molecular level upon a process which usually cannot be satisfactorily reproduced in laboratory animals; at the same time the physiological effect sought is only being exerted in a minor way and thus may only become apparent through statistical analysis of relatively large numbers of observations. It is much easier to study large enough numbers epidemiologically than in a laboratory.

In more specific terms, a peptic ulcer can be looked upon as arising when agents acting 'aggressively' upon the gastric or dùodenal mucosa overcome those acting 'defensively'. The former, it is generally agreed, are hydrogen ions and the pepsins, the latter the mucosal barriers. In the duodenum, the alkaline pancreatic juice also acts defensively and, in the stomach, refluxed bile may act aggressively by causing gastritis and weakening the mucosal barrier (Du Plessis 1965).

The effect of smoking upon hydrogen ion secretion has been widely investigated, as has that of nicotine – the principal pharmacological substance in tobacco. The results are conflicting, but taking them overall most reviewers, including ourselves, conclude that neither smoking nor nicotine, under acute or chronic circumstances, stimulates consistently an increased hydrogen ion secretion (Bennett 1972, Solomon & Jacobson 1972, Whitecross *et al.* 1974). There have been fewer studies of total gastric pepsin secretion in smokers, or during smoking, or after nicotine administration, but again there is no consistent evidence of an increased total pepsin output in the basal or stimulated gastric secretions in relation to smoking (Cooper & Knight 1956, Debas *et al.* 1971, Wilkinson & Johnston 1971, Whitecross *et al.* 1974). Mucus production, too, remained unaltered in normal subjects, and in ulcer patients who were smokers, during the smoking of four cigarettes hourly (Whitecross *et al.* 1974). A considerable body of careful investigations has therefore failed to explain the connection of smoking with peptic ulcer, at a physiological level, in terms of hydrogen ion, total pepsin, or mucus secretion.

So far as the duodenal mucosa is concerned, an effective increase in its exposure to gastric hydrogen ions and pepsins would occur if the total quantity of secreted alkaline pancreatic juice, which neutralizes the hydrogen ions, were to fall. Since 1972, four studies have been made in man of the effect of smoking on pancreatic bicarbonate secretion (Bynum *et al.* 1972, Bochenek & Koronczewski 1973, Brown 1976, Murthy *et al.* 1977), or on intraduodenal pH. All show decreases of bicarbonate output, a unanimity which is impressive, despite Wormsley's (1978) criticisms, when contrasted with the conflicting results from the studies of gastric hydrogen ions and total pepsins. Happily, too, most animal experiments have also shown an inhibition of pancreatic bicarbonate secretion during intravenous administration of nicotine. The practical effect in man is that smoking may lower the duodenal pH. The bulbar pH remained below 3.5 for significantly longer during smoking, as compared with the basal state, in normals and in patients with duodenal ulcer; the effect was greatest in hypersecretors of hydrogen ion (Murthy *et al.* 1978).

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This effect of smoking upon pancreatic secretion, which must, on the evidence, be accepted, cannot of course explain the increased incidence of gastric ulceration in smokers. Clearly other factors are operating here. One of these factors, it has been postulated (Read & Grech 1973) is the reflux of bile from the duodenum into the stomach. The refluxed bile causes gastritis which in turn lowers mucosal resistance to (presumably) hydrogen ions and pepsins. It is known that gastritis is more common in smokers than in nonsmokers (Edwards & Coghill 1966), and that bile-staining is more common in gastric aspirates collected during smoking than when not smoking (Whitecross *et al.* 1974). There is also both manometric (Valenzuela *et al.* 1976) and radiological (Read & Grech 1973) evidence that smoking causes incompetence of the pyloric sphincter leading to gastroduodenal reflux. This hypothesis, furthermore, has the attraction of accounting to some extent for the fact that gastric ulceration occurs predominantly in the juxtapyloric area of the stomach. However, gastric mucosa exposed to bile alone does not develop gastritis (Byers & Jordan 1962), but it does if exposed to jejunal contents (Delaney *et al.* 1970). The latter group therefore suggest that refluxed pancreatic enzymes may be important in initiating gastric mucosal damage, acting at times when the intragastric pH is neutral, and that gastric peptic activity would then increase the damage further during periods of low intragastric pH.

Our own work indicates a further factor that is operating in both gastric and duodenal ulcer. We find that a qualitative alteration in pepsin secretion occurs in smokers with peptic ulceration. It has been known for some years that there is more than one pepsin in human gastric juice (Taylor 1956) and that one of these, pepsin 1, is present in increased amount in both gastric and duodenal ulcer (Taylor 1970). In a retrospective study (Walker & Taylor 1979) we have found that significantly more cigarette smokers with peptic ulceration (72.5%) secrete pepsin 1, in a concentration of 22 μg/ml or more, following pentagastrin or histamine than do nonsmokers with ulceration (51.2%). The magnitude of this difference was similar for men with duodenal ulcer, women with duodenal ulcer and all patients with gastric ulcer. There was no significant association between smoking and pepsin 1 secretion among 74 patients without ulceration. Higher concentrations of pepsin 1 were found among ulcer patients smoking 6 to 15 cigarettes daily than among heavier smokers.

These observations must be interpreted in a somewhat wider context. Patients with gastric ulcer differ from normal subjects not in their total pepsin secretion (as measured by digestion of haemoglobin), but in secreting a greater proportion of it as pepsin 1. The same is true of those patients with duodenal ulcer in whom the total pepsin secretion is normal; in those in whom it is raised, pepsin 1 contributes greatly to the increase. Pepsin 1 is also secreted in increased amount in patients with acute stress (Walker & Taylor 1977) who are, as a group, prone to acute peptic ulceration, and in nonsecretors of ABH antigens (Waft *et al.* 1979), in whom there is an increased incidence of peptic ulcer.

Present work hints at the way in which pepsin 1 possibly exerts a pathological effect. Both pepsin 1 and pepsin 3 degrade collagen *in vitro* at acid pH, but pepsin 1 is the more active in this respect (Etherington *et al.* 1980). The gastric juice of patients with peptic ulcer may thus have a greater capacity to digest the collagen of the gastrointestinal mucosa than has normal gastric juice.

Smoking thus has at least three pathophysiological effects on the stomach and duodenum. It diminishes the secretion of pancreatic bicarbonate so that the pH in the first part of the duodenum may become more acid than normal, enabling pepsins 1 and 3 to exert more readily than in nonsmokers their proteolytic and collagen-degrading effects on the duodenal mucosa. Smoking is also associated with increased gastroduodenal reflux of bile, which affects the mucosal surface of the stomach in such a way that the pepsins, particularly pepsins 1 and 3, may attack it the more easily. Thirdly, smokers with peptic ulcer have an increased concentration of the collagen-degrading pepsin 1, when compared with nonsmoking ulcer patients. Although certain facts remain unexplained, such as the absence of an increased pepsin 1 secretion in non-ulcer subjects who smoke, the combination of the three effects goes some way to explaining how smoking promotes peptic ulceration in the stomach and in the duodenum and then, by the same actions, prevents the ulcers from healing.

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Oestrogens and host resistance[1]

The effects of oestrogens during pregnancy and the menstrual cycle can be seen in women and in many animals during oestrous. Such effects can often be mimicked by the administration of oestrogen. The production of oestrogen increases a thousandfold in human pregnancy (Beling 1977, Levitz & Young 1977); marked increases also occur at oestrous in animals. However, even in pregnancy the concentrations of oestrogens are lower than those used in many, especially of the early, experiments on the biological effects of oestrogens, including those concerned with the immune systems.

In searching for a means of unifying some of the immunological phenomena of pregnancy, and the sex differences in morbidity and mortality due to infection (Washburn *et al.* 1965), it seemed rational to speculate on the possible effects of oestrogen on host resistance. It is only practicable to select areas in which the broad outline of facts seem to suggest a pattern. It is also possible to identify more limited areas in which evidence seems to justify a testable hypothesis. One example of the latter type of area appears to be the peroxidatic bactericidal mechanisms of nonspecific host resistance.

In order to discuss the problem of the immunobiology of pregnancy at least three broad categories are used. One is specific immunity which is related to host-tolerance of foreign compounds; the second is nonspecific immunity or nonspecific host resistance; and the third is inflammation. An apparently superficial overview is necessary since all three processes can be interrelated.

An outline of the clinical changes in host resistance during pregnancy in humans and other animals shows that alterations can occur although there is not a marked increase in infections during pregnancy. The improvement of rheumatoid arthritis during pregnancy is widely accepted. Despite suggestions that the corticosteroids might be involved in this modulation of the inflammatory response, there is little definite evidence of such a mechanism despite extensive work to test this possibility. The clinical manifestations of syphilis are reduced in pregnancy. In contrast, systemic lupus erythematosus deteriorates in pregnancy. Crohn's disease, a chronic inflammatory disease of unknown aetiology, is unaltered in pregnancy but does respond like rheumatoid arthritis to pharmacological doses of corticosteroids (Barnes 1974). A further condition in which chronic inflammation can be involved is sarcoidosis, which is commonest in sexually mature females. However, some aspect of hypersensitivity may be involved in this condition in view of the commonly associated erythema nodosum. Hypersensitivity can also be involved in asthma, which shows no change in pregnancy.

In man viral infections, including vaccination with live attenuated strains, appear to be enhanced by pregnancy (Fleming 1975, Lowrie *et al.* 1977). The years of epidemic poliomyelitis in the USA provided considerable evidence of the increased susceptibility of pregnant women to this disease (Priddle *et al.* 1952, Rindge 1957).

In experimental animals mice normally resistant to foot and mouth disease become susceptible in pregnancy, and in mice the susceptibility to coxsackie viruses increases with gestational age (Lowrie *et al.* 1977). The available evidence therefore suggests that virus infections can produce marked effects at times of raised oestrogen production.

The effects of bacterial infection in pregnancy can be enhanced. Acute pyelonephritis is more common in pregnancy than at other times, affecting about 4% of pregnant women. However,

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