A STUDY OF

MUCOSAL RESISTANCE

IN

GASTRIC ULCERATION

INDEX

The magnitude of peptic ulceration as a social, economic and community problem has recently been stressed by Blumenthal (1968), who estimated that in 1963 in the United States of America the annual cost in terms of loss in earnings from peptic ulcer was $463 million. Peptic ulceration was the twelfth most common disease responsible for absenteeism from work, and ranked fifteenth in the causes of death for 1965. Furthermore, Blumenthal demonstrated that the prevalence of this disease increased from 14.4 per thousand population per year in 1957-1959 to 19 per thousand per year in 1963-1965. The economic loss from this disease is thus likely to increase.

Peptic ulcer disease was first described by Cruveilhier in 1829 and in 1970, despite manifold theories about the aetiology of this disease, its cause remains unknown. It is not surprising therefore, with therapy directed not at the cause but at manifestations of the disease, that overall the treatment of peptic ulceration is unsatisfactory. Indeed, there is no definitive proof that medical treatment in the long term has a favourable influence on the natural history of the disease, and a high incidence of post-operative problems such as malabsorption, various post-prandial syndromes and recurrent ulceration frustrates the surgical treatment of peptic ulceration. It is apparent that the pathogenesis of the disease must be elucidated if any major advance in the medical treatment of peptic ulceration is to be made.

Chronic peptic ulceration results from an imbalance between aggressive and defensive factors acting on the gastrointestinal mucosa, and at the present time many differences in occurrence and behaviour indicate that gastric and duodenal ulcers should be considered independent diseases (Figure I). Duodenal ulceration is associated with increased acid and pepsin secretion, or increase in aggression. The lack of any demonstrable increase in aggressive factors in primary chronic gastric ulceration has led to the assumption that the ulcer results from diminished mucosal resistance.

Mucosal resistance is provided by two major components - mucus produced by and covering the epithelial cells in the stomach, and the integrity of the epithelial cell layer or mucosa itself. There is no proof that mucus production is altered in patients with primary chronic gastric ulcers, and diminished mucosal resistance resulting from impaired mucus production is unlikely to be an important cause of ulcer formation. However a high incidence of extensive inflammation in the gastric mucosa of patients with chronic gastric ulceration has been widely reported, and this suggests that an abnormality of the mucosa may be implicated in the mechanism of gastric ulcer formation. Histological abnormalities do not per se imply functional abnormality, and investigation of the functional integrity of the gastric mucosa in this disease is therefore necessary.

To date the investigation of the functional capacity of the gastric mucosa in patients with chronic gastric ulceration has been hindered by a lack of suitable techniques. Considerable knowledge of cellular metabolism has been gained over the past two decades by the introduction of radioisotopic techniques into medical research, and indeed the recognition of the rapid proliferation rate of gastrointestinal tissue is in large part attributable to such techniques. Unfortunately many radio-isotopes are potentially hazardous and their application to the study of human subjects is consequently limited by ethical and moral principles. To date therefore, radioisotopic techniques have been largely confined to the investigation of cellular metabolism in animals. Such knowledge from an animal model may not necessarily be validly extrapolated to man (McDonald, Trier and Everett, 1964). Techniques not involving the administration of radioactive substances must be applied to the study of biochemical function of gastrointestinal mucosa if knowledge of the functional integrity or resistance of the gastric mucosa in patients with chronic gastric ulcer disease is to be advanced.

The purpose of the study described in this thesis was to investigate mucosal resistance at a cellular level, particularly in relation to chronic gastric ulceration. The fact that gastrointestinal tissue was known to have a high rate of cellular proliferation suggested that study of nucleic acid

metabolism with its relationship to cell division and protein synthesis might be a rewarding area for investigation. A possible relationship between the activity of some of the enzymes involved in the synthesis of the purine ribonucleotide precursors of nucleic acid, and the rate of nucleic acid metabolism had been previously reported (Murray and Nicholls, 1968). It was considered that investigation of these enzymes in the gastric mucosa of patients with chronic gastric ulceration might reveal a functional abnormality if one were present.

The selection of an animal model for assessment of the purine nucleotide biosynthetic enzymes was difficult because of the low incidence of chronic gastric ulceration in laboratory animals. However, acute gastric erosions or ulceration have been consistently produced by stress restraint, and in this group Imondi, Balis and Lipkin (1968) have described abnormalities of nucleic acid metabolism. Although it was recognised that the acute gastric mucosal lesions in animals were not directly comparable to chronic gastric ulceration in man, a similar model was selected to assess whether the level of activity of selected purine nucleotide biosynthetic enzymes reflected the rate of nucleic acid synthesis.