Progress report

In ‘defence’ of the gastric mucosa

For many years physiological properties within the body that lead to or prevent ulceration of gastric and duodenal mucosa have been thought of as being ‘aggressive’ or ‘defensive’ in nature. Peptic ulcer has been assumed to develop when the summation of aggressive factors is greater than defensive, and a past concept has assumed that an increase in the latter or decrease in the former would lead to a decreased propensity of the mucosa to ulcerate.

The reasons for the resistance of normal gastric mucosa to self-digestion have long been sought. It is known that exposure of intestinal mucosa to gastric juice can induce the formation of ulcerations\(^1,1^a\). Possibly back diffusion of acid into gastric mucosa can do the same. Are there any specific properties of the gastric mucosa that might contribute to a defence against ulceration, and, in particular, might it be possible to enhance any of these properties? A number of factors that are believed to act to defend the mucosa have been observed in the past. For example, well known physiological mechanisms that inhibit excessive gastric secretion in response to the presence of gastric juice in gastric antrum or duodenum have been observed\(^2,3\). A variety of experiments have also suggested that nutritional factors and normal intake of dietary protein\(^4,5\) as well as growth hormone\(^6\) help to maintain this resistance of the mucosal cells against ulceration.

Of particular interest for many years has been the postulated ‘first line of defence’ against mucosal injury, the mucus layer provided by the epithelial cells of the stomach\(^7\). This layer of mucus, together with the ‘second line of defence’, the healthy epithelial cells themselves, have been thought to play a significant role in defence of the mucosa against injury and ulceration. The mucus-producing epithelial cells lining the gastric pits and surface of the mucosa are believed to supply mucus quite rapidly to produce a coat protecting the cells against injury.

In recent years additional elements that relate to the production of mucus and the epithelial cells themselves (the ‘first’ and ‘second’ lines of defence) have been developed. New information about how these cells are produced, and how they develop and mature in the gastric mucosa has emerged. This information is pertinent to an analysis of how the epithelial cells are able to remain viable in the gastric milieu. This information has indicated a dynamic and rapid life cycle of the mucus-producing gastric epithelial cells in man and other mammalian species and a necessity for continued cell replacement to offset rapid extrusion that takes place due to a limited life span of the cells\(^8\). These rapidly proliferating and differentiating mucus-producing epithelial cells of both gastric and intestinal mucosa have a life span of only a few days. When new cells are produced below the surface of the gastric mucosa and in the crypts of intestine they undergo very rapid morphological and biochemical differentiation as they quickly move to the surface to be extruded. In the stomach, these cells are produced from progenitor elements located in the
neck and isthmus regions of the gastric pits. A small number of the latter cells also give rise to parietal zymogen cells at a slower rate.

As the epithelial cells undergo normal differentiation and migrate to the gastric surface, new metabolic activities emerge and others become inactive. Among the former are changes in the types of mucosubstances developing in these cells. In mucus-producing cells of this type the protein moiety of the mucus is believed to be produced by ribosomes associated with the endoplasmic reticulum, then transported to the Golgi complex of the cell where mucigen granules form. During its passage through the Golgi complex the secretion is believed to undergo condensation, sulphation, and the carbohydrate moiety is added. Mucus which is discharged from a cell may attach to the cell surface or move away from the cell to become part of the general secretion bathing the epithelium.

During the differentiation of gastric epithelial cells other areas of metabolic activity decrease simultaneously with the activation of mucus-producing pathways. The most important of these involves the decrease that takes place in the DNA synthetic apparatus, and in the entire chain of events leading to mitosis and cell replication. Among the metabolic pathways related to DNA synthesis that have been observed to decrease in intestinal cells during normal differentiation is activity of the important nucleic acid precursor enzyme thymidine kinase. Before and during the development of neoplastic lesions of stomach and colon metabolic activities related to DNA synthesis persist in epithelial cells undergoing abnormal differentiation. Migrating epithelial cells develop an enhanced capacity to proliferate in the mucosa. This early breakdown in normal repression of the DNA synthetic apparatus is followed at later stages of neoplastic development by a failure of additional differentiation-specific nucleic acid pathways to develop. In liver and other tissues other nucleic acid enzymes concerned with DNA synthesis decrease in activity when regeneration stops. With respect to the development of the normal epithelial cell lining of the mucosa, therefore, the complex factors that normally lead to cessation of proliferation also simultaneously lead to the continued rapid production, differentiation, and migration to the surface of new, well differentiated mucin-producing epithelial cells in all areas of mucosa.

Is it possible that these aspects of cell growth might be related to the development of ulceration of the gastric or duodenal mucosa? Recent studies support the conclusion that these factors have a close connexion with the pathogenesis of peptic ulceration. For example, several studies have demonstrated that an inhibition of DNA synthesis and epithelial cell proliferation precede and accompany the development of experimental restrain-stress-induced erosions in gastric mucosa of rodents. A loss of RNA from these cells also develops, and this could be related to a decrease in the protein moiety needed for mucoprotein synthesis during ulcerogenesis. During stress cell replication in the stomach is decreased. As gastric erosions begin to form, it might be expected that cell replication would increase (as occurs for example after wounding the skin to initiate wound healing). However, with continued stress, the rate of gastric cell replication not only does not increase nor remain normal but actually remains decreased. Other evidence of cell damage and decreased mucus appears. These cells, having a limited life span, continue to be extruded. In patches of mucosa where cell replication cannot keep up with the extrusion rate, and with continued contact...
of the cells with the gastric secretions, erosions begin to appear in the gastric mucosa.

Recent studies with carbenoxolone, which has been used successfully in the treatment of peptic ulcer disease\textsuperscript{17}, have indicated that both mucus production and the rate of flow and extrusion of gastric epithelial cells from the mucosa are influenced by the compound. This triterpenoid compound appears to have an action by direct contact with mucus-producing epithelial cells in the gastric or duodenal mucosa, and is rapidly absorbed into the blood. In man it is excreted in bile as the glucuronide\textsuperscript{18}. Increased amounts of mucus have been reported after contact of carbenoxolone and mucosa, and this is believed in some way to offer protection to immature cells at the base of gastric erosions that are needed for regeneration\textsuperscript{19}. Since the compound is absorbed largely from stomach and is very extensively bound to plasma proteins before being rapidly excreted, its action to induce glycoprotein synthesis may occur on passage of the drug through the mucosa during its absorption\textsuperscript{18}.

Carbenoxolone has been used both in man and experimental animals. Recent animal experiments have shown that the growth of several varieties of gastric erosions are inhibited by treatment with carbenoxolone\textsuperscript{20, 21}. Among experimental models, the incidence and severity of restraint-stress-induced erosions were decreased by pretreatment with carbenoxolone, coincident with the appearance of excessive mucosubstance in the gastric epithelial cells\textsuperscript{21}. Further attempts to evaluate whether a change in the proliferative characteristics of the gastric epithelial cells had taken place indicated that this was so. In the rodent stomach, under the influence of carbenoxolone, fewer cells entered the proliferative cell cycle. At the same time, the rate of removal of cells from the mucosa was diminished and the cells had a longer life span\textsuperscript{22}. Under restraint-stress in rodents, the rate of loss of thymidine-\textsuperscript{3}H-labelled epithelial cells from the gastric mucosa also was decreased with carbenoxolone treatment compared with non-treated controls, indicating that under acute stress the gastric epithelial cells had a longer life span\textsuperscript{23}.

Thus, the appearance of increased amounts of mucus and a change in the proliferative activity of the cells appeared to take place simultaneously with the application of carbenoxolone. Whether the induction of enzyme activities connected with mucoprotein synthesis might be associated with the system of regulatory controls governing the initiation or cessation of DNA synthesis in these cells or to aldosterone-like activity of the compound\textsuperscript{24} is not known.

The reasons for activation and inactivation of regulatory signals leading to the onset and cessation of proliferative activity are poorly understood at this time and have been only partially defined. In order for cells to continue to re-enter the proliferative cycle and make new DNA, specific RNAs and proteins are needed, in addition to other requirements\textsuperscript{8}. The induction of enzymes needed for mucoprotein synthesis may preclude the development of some of these. During cell differentiation and the cessation of DNA synthesis other characteristic enzyme activities involved in the synthesis of nucleic acid precursor molecules also increase. These include purine nucleoside phosphorylase and pyrophosphate phosphoribosyl transferases, which appear to be involved in a number of metabolic activities and these may include the re-utilization of nucleic acid precursors\textsuperscript{13, 25}. Differing regulatory controls also appear to be built into the cells during differentiation to change the expression of enzyme activities\textsuperscript{26}. Among recent factors that also have been
connected with the initiation of DNA synthesis are changes in membrane potential, and a required secretion of cell products.\textsuperscript{27,28}

These dynamic properties of the cell membranes may well be responsible for the initiation of internal signals needed for replication. As cells move towards the mucosal surface, they may also selectively respond to external signals in the local environment to initiate replication and maturation. It is in this area that a change in accumulation or secretion of mucus induced by carbenoxolone may find common ground with the modification of cell replication that carbenoxolone induces.

Thus, it appears that a single agent can influence several of the characteristics of proliferating and differentiating gastric epithelial cells. By doing so, the agent seems to enhance the property of the cells previously thought by Hollander to be the first line of defence, the mucus coat of the cells, and at the same time increase the life span of the second defence, the maturing epithelial cells themselves.

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