artificial interference with regulatory cytokine pathways using gene knockout technology has, in many cases, resulted in animal forms of chronic intestinal inflammation which resemble human inflammatory bowel disease.⁷ Moreover, recent studies have shown that a single infusion of a chimeric monoclonal anti-TNF antibody was an effective short term treatment in many patients with moderate to severe Crohn's disease.⁸ However, despite such encouraging results, the complexity of cytokine networks and their overlapping roles leads one to intuit that the notion that interference with a single cytokine could cure all cases of inflammatory bowel disease may be naive and possibly dangerous in the long term.

FUTURE DIRECTIONS

Localisation of cytokine production to individual cell populations and different stages of stimulation will be fundamental to understanding how they might be ultimately manipulated in pathogenic situations. It is becoming increasingly clear that intestinal T cells are highly heterogeneous with regard to TCR and co-receptor expression, activation status and origin.⁹⁻¹¹ It is likely that their cytokine profiles will be equally individual. Lambrechts *et al* found that virtually all IL-4 and IFN- γ secreting cells in the lamina propria were CD4+. In the epithelium, IFN- γ elaboration was found in CD8+ populations as well as CD4+. Further isolation of various subpopulations of lymphocytes from both intestinal compartments and comprehensive analysis of their cytokine production potential will be required in order to understand their function. TNF, IL-12, IL-18, and TGF- β will be particularly interesting cytokines to study from this point of view. Cytokine production by cells other than lymphocytes will also have important functional implications—for example, it already has been shown that epithelial cells elaborate IL-6, IL-10 and, more recently, IL-7.¹² Development of the technical ability to analyse coexpression of two or more cytokines and changes in relative proportions of the cytokine cocktail produced by individual subpopulations will lead to more accurate mapping of cytokine networks and their influences. However, a two-dimensional fixed chart could only

ever be a limited representation of this plastic, interdependent system. Some sort of a multidimensional, dynamic map will be required to make accurate predictions of how the intestinal immune response might be manipulated by influencing individual cytokine expression. Thus, computer modelling of cytokine networks may lead to successful prediction of the small changes in individual components of cytokine networks required for disease treatment and prevention while maintaining homeostasis of the gastrointestinal immune system.

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Intestinal metaplasia and the squamocolumnar junction: what does it all mean?

In theory, the diagnosis of Barrett's oesophagus should be fairly simple, namely the presence of intestinal metaplasia anywhere in the tubular oesophagus. However, recognising where the tubular oesophagus ends and the saccular stomach begins is fraught with difficulty. The precise junction may be difficult to identify endoscopically because of the presence of a hiatus hernia, inflammation and some disassociation between the squamocolumnar junction and the lower oesophageal sphincter zone in normal individuals. Histologically, the squamous mucosa of the oesophagus accurately defines this area, but distinguishing normal gastric cardia and metaplastic changes of the distal oesophagus may be difficult. Normally, the mucosa of the cardia is composed of tightly packed mucus secreting glands with a lamina propria devoid of any significant inflammatory

component. On occasion, biopsy specimens from the cardia show an increase in the amount of acute and chronic inflammatory cells, a condition termed carditis. The cardia can also have associated areas of intestinal metaplasia with goblet cells, histologically similar to the well described intestinal metaplasia in the distal stomach or classically defined as Barrett's oesophagus when located in the tubular oesophagus. Finally, structures just do not sit still in the oesophagus during endoscopy, making precise location and biopsy even more difficult. Thus, it is difficult to know in every case whether the intestinal metaplasia is from the distal oesophagus or from the cardia.

The classic definition of Barrett's oesophagus requiring the presence of at least 2-3 cm of intestinal metaplasia above the oesophagogastric junction, protected us from some of these difficulties. However, the evolving concept of short segment Barrett's oesophagus, namely specialised columnar epithelium lining less than 2-3 cm of the distal oesophagus, now raises the question as to where to obtain biopsy specimens in patients undergoing upper endoscopy. This controversy was further intensified in 1994 after Spechler and colleagues published their study of consecutive patients

referred for elective upper endoscopy for a variety of upper gastrointestinal symptoms.¹ All patients had two biopsy specimens taken from the columnar side of the oesophagogastric junction, even if there was 3 cm or less of endoscopically apparent Barrett's epithelium. Of the 142 patients studied, two (1%) had endoscopic evidence of Barrett's oesophagus, whereas 26 (18%) had intestinal metaplasia below a normal appearing squamocolumnar junction. The groups did not differ significantly in the frequency of symptoms and endoscopic signs of gastro-oesophageal reflux. However, patients with the specialised columnar epithelium at the normal oesophagogastric junction were predominantly white men, the same demographic pattern as seen in conventional length Barrett's oesophagus. Subsequently, several groups have identified short segment Barrett's oesophagus in 8–10% of almost 500 consecutive patients undergoing upper endoscopy in various settings.^{2–4} Male sex usually predominates and reflux symptoms are common. The study by Dias Pereira *et al* in this issue (see page 659) confirms these observations while suggesting that the prevalence of short segment Barrett's oesophagus does not increase with advancing age, an observation somewhat different from that in classic Barrett's oesophagus.

Could all of these simply be intestinal metaplasia of the gastric cardia? The answer is still evolving but several issues were tackled in recent studies. How common is intestinal metaplasia of the cardia? In an unselected group of patients undergoing endoscopy in a Veteran's Affairs Hospital, Morales and colleagues³ found intestinal metaplasia of the cardia in 24 (23%) of 104 patients, a prevalence similar to the 25% reported by Dias Pereira and colleagues. Others report similar findings but with a lower prevalence. Hirota and coworkers⁵ found intestinal metaplasia of the cardia in only 47 (5.3%) of 889 patients, whereas in our recent study of 86 patients undergoing elective endoscopy, we found intestinal metaplasia of the cardia in 9%.⁶ What are the demographics of patients with intestinal metaplasia of the cardia? Men predominate in some populations, but others find that women are common. Most studies find a lower frequency of reflux symptoms. In fact, only two of eight patients with intestinal metaplasia of the cardia in our study had reflux symptoms.⁶ Finally, most studies find intestinal metaplasia of the cardia predominantly in an older population. Are there any histological clues to the aetiology of intestinal metaplasia of the cardia? Nearly all patients with intestinal metaplasia of the cardia have associated carditis. Despite an intriguing hypothesis that carditis is an inflammatory change that occurs as a consequence of gastro-oesophageal reflux disease,⁷ this seems not to be the case. For example, we found carditis in 41% of our control population compared with 40% of patients with reflux.⁶ Rather, *Helicobacter pylori* infection seems to be the cause of most cases of carditis and associated intestinal metaplasia of the cardia. Morales *et al* found that 68% of patients with intestinal metaplasia of the cardia were infected with this organism.³ Likewise, we found that intestinal metaplasia of the cardia was more common among controls (22%) than patients with reflux (3%). All eight of these patients has associated carditis, seven with biopsy and/or serological evidence of *H. pylori* infection, and six had intestinal metaplasia elsewhere in the stomach. What is the association between Barrett's oesophagus and

intestinal metaplasia of the cardia? Morales and colleagues³ found intestinal metaplasia of the cardia in two (18%) of 11 patients with Barrett's oesophagus. Weston and colleagues⁸ found intestinal metaplasia of the cardia in eight (7%) of 119 patients with Barrett's epithelium. Interestingly, it was encountered in six (10%) of 59 patients with short segment Barrett's oesophagus and only two (3.3%) of 60 patients with >2 cm of Barrett's epithelium. Thus, short segment Barrett's oesophagus and intestinal metaplasia of the gastric cardia may overlap and may be an artefact of the true site of biopsy at the oesophagogastric junction.

What does this all mean? At the time of endoscopy, landmarks should be carefully defined and if the squamocolumnar junction is above the level of the oesophagogastric junction, biopsy samples should be obtained. Helpful findings for short segment Barrett's oesophagus include a straight and regular squamocolumnar junction displaced upwards in relation to the gastro-oesophageal junction by <3 cm or an irregular squamocolumnar junction with eccentric tongues of red mucosa extending above this junction. If intestinal metaplasia is present, the patient is considered to have Barrett's oesophagus and should be placed on an endoscopic surveillance programme as dysplasia and adenocarcinoma may develop in these patients. In clinical practice, biopsy samples should not be taken routinely below a normal appearing squamocolumnar junction. Goblet cells found at this level are probably secondary to intestinal metaplasia of the gastric cardia, probably resulting from chronic *H. pylori* infection. This can be confirmed by serological studies for *H. pylori* as well as biopsy of the more distal antrum and body. The implications for endoscopic surveillance in patients with intestinal metaplasia of the cardia is unknown at this time. However, it is intriguing to speculate that the increase in adenocarcinoma at the oesophagogastric junction may be secondary to two processes. That is, an increased prevalence of Barrett's oesophagus in an aging white male population as well as an increase in the prevalence of multifocal atrophic gastritis and intestinal metaplasia which can include the cardia secondary to *H. pylori* infection in aging individuals, both male and female.

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