

Quality of ulcer healing in gastrointestinal tract: Its pathophysiology and clinical relevance

Tetsuo Arakawa, Toshio Watanabe, Tetsuya Tanigawa, Kazunari Tominaga, Yasuhiro Fujiwara, Ken'ichi Morimoto

Tetsuo Arakawa, Toshio Watanabe, Tetsuya Tanigawa, Kazunari Tominaga, Yasuhiro Fujiwara, Ken'ichi Morimoto, Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka 545-8585, Japan

Author contributions: Arakawa T performed all the managements and decision making to conduct animal experiments and clinical studies, and prepared this manuscript; Watanabe T and Tanigawa T performed most of the animal experiments; Tominaga K and Fujiwara Y performed most of the human study of peptic ulcer disease; Morimoto K performed the human study of Crohn's disease.

Correspondence to: Tetsuo Arakawa, MD, PhD, Professor, Dean and Chairman, Department of Gastroenterology, Osaka City University Graduate School of Medicine, 1-4-3 Asahimachi, Abeno-ku, Osaka 545-8585,

Japan. arakawat@med.osaka-cu.ac.jp

Telephone: +81-6-66453810 Fax: +81-6-66463413

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Abstract

In this paper, we review the concept of quality of ulcer healing (QOUH) in the gastrointestinal tract and its role in the ulcer recurrence. In the past, peptic ulcer disease (PUD) has been a chronic disease with a cycle of repeated healing/remission and recurrence. The main etiological factor of PUD is *Helicobacter pylori* (*H. pylori*), which is also the cause of ulcer recurrence. However, *H. pylori*-negative ulcers are present in 12%-20% of patients; they also recur and are on occasion intractable. QOUH focuses on the fact that mucosal and submucosal structures within ulcer scars are incompletely regenerated. Within the scars of healed ulcers, regenerated tissue is immature and with distorted architecture, suggesting poor QOUH. The abnormalities in mucosal regeneration can be the basis for ulcer recurrence. Our studies have shown that persistence of macrophages in the regenerated area plays a key role in ulcer recurrence. Our studies

in a rat model of ulcer recurrence have indicated that proinflammatory cytokines trigger activation of macrophages, which in turn produce increased amounts of cytokines and chemokines, which attract neutrophils to the regenerated area. Neutrophils release proteolytic enzymes that destroy the tissue, resulting in ulcer recurrence. Another important factor in poor QOUH can be deficiency of endogenous prostaglandins and a deficiency and/or an imbalance of endogenous growth factors. Topically active mucosal protective and antiulcer drugs promote high QOUH and reduce inflammatory cell infiltration in the ulcer scar. In addition to PUD, the concept of QOUH is likely applicable to inflammatory bowel diseases including Crohn's disease and ulcerative colitis.

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Key words: Quality of ulcer healing; Peptic ulcer disease; Recurrence; Prostaglandin; Cytokines; Growth factors

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BIOGRAPHY

Professor Tetsuo Arakawa (Figure 1) received his MD

and PhD degrees from Osaka City University Graduate Medical School, Japan. He was Visiting Research Scholar and Professor at the University of California, Irvine (1990) and the University of Arizona, Tucson, AZ, United States (2000). He is currently Dean and Chairman, Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan. His Curriculum Vitae lists 404 original articles, 421 review articles, 275 book chapters, 24 edited books, prestigious academic awards and honors, and numerous presentations at national and international meetings, including American Gastroenterological Association (AGA), American College of Gastroenterology (ACG), Pasteur Institute and others (over 300 presentations). He has been President/Governor: Japanese Gastroenterological Association, Japanese Society of Gastrointestinal Endoscopy, Japanese Society of Ulcer Research, International Conference on Ulcer Research, Japanese Society of Neurogastroenterology, Japanese Society of Gastroenterological Immunology, and Japanese Society of Capsule Endoscopy chaired numerous sessions during American Gastroenterological Association Meetings and is member of 10 national/international societies, including Fellow of AGA and Fellow of ACG. His research interests cover numerous areas of gastroenterology, endoscopy and pathophysiology; he significantly contributed to the concept of cytoprotection, molecular mechanisms of gastric ulcer healing, mechanisms of anti-ulcer drugs action and translation of basic research to clinical application.

INTRODUCTION

Prior to the introduction of *Helicobacter pylori* (*H. pylori*) eradication treatment, peptic ulcer disease (PUD) had been a chronic disease affecting 5%-10% of the population with a cycle of repeated healing/remission and recurrence. The treatment aimed at eradication of *H. pylori* has changed the life cycle of this disease and the prevalence rate has dramatically decreased. However, the dictum “no *H. pylori*, no ulcer” is over-rated^[1]. *H. pylori*-negative PUD exists, similar to PUD in nonusers of nonsteroidal anti-inflammatory drugs (NSAIDs). This PUD is referred to as non-*H. pylori*, non-NSAIDs ulcer or idiopathic PUD (IPUD)^[2]. A prevalence rate of IPUD has been reported as 12%-20%, suggesting that IPUD is not rare^[2]. A recent report has shown the increase in the prevalence of IPUD^[3], however this remains controversial^[4].

The recurrence rate of IPUD is higher than *H. pylori* and/or NSAID-associated PUD^[5] and their management is more difficult and more costly compared to other ulcers^[5]. The recurrence rate of ulcer may be related to quality of ulcer healing (QOUH). The pathogenesis of poor QOUH may be the underlying cause of the refractoriness and ulcer recurrence. In addition to PUD, the concept of QOUH may be applicable to inflammatory



Figure 1 Tetsuo Arakawa, MD, PhD, Dean, Osaka City University Graduate School of Medicine, 1-4-3 Asahi-machi, Abeno-ku, Osaka 545-8585, Japan.

bowel disease (IBD), which is also a chronic and recurrent ulcer disease. It is likely that in order to obtain a permanent ulcer healing and remission, the high QOUH is necessary for any type of ulcer disease.

MYSTERY OF ULCER RECURRENCE: PAST HISTORY OF PATHOPHYSIOLOGY

Ulcer recurrence has long been thought to be an unavoidable feature of PUD, and therefore, maintenance treatment has been necessary to prevent recurrence. *H. pylori* is a major cause of both PUD and its recurrence. The bacteria are, however, not the only cause of ulcer recurrence, and still there are a certain number of patients with PUD not related to *H. pylori* and NSAIDs, referred to as IPUD^[2,4]. To prevent recurrence of IPUD, the investigations examining the pathophysiology of ulcer recurrence are important.

Oi *et al*^[6] have proposed the double-regulation theory to explain why PUD favors the gastric angle. They examined many stomachs with ulcers that had been operated upon, and found that the ulcer site was usually at the interphase of the distal side of the glandular borderline (mucosal rule) and line of distortion of movement (muscular rule). This may be the point of combination of the mechanical tension and exposure to high concentrations of acid in the pyloric gland area. The latter mucosa has a weaker resistance to acid compared to the fundic gland area. This theory may also explain why the ulcer often recurs at the same or neighboring site of a previous ulcer. This theory, however, does not fit with duodenal or gastric ulcer at other sites. Therefore, it is important to determine how the ulcer recurs.

Pan *et al*^[7] have reported that the recurrence of healed duodenal ulcer depends on the histological maturity of regenerated mucosa. They have indicated that the cause of ulcer recurrence may be related to the abnormalities of the scar of healed ulcer, leading to the concept of QOUH^[7]. Takagi *et al*^[8] have developed a chronic gastric ulcer model in rats by topical application of acetic acid from the serosal side of the gastric glandular borderline. This model closely mimics human PUD both in histol-

Table 1 Definition and criteria of quality of ulcer healing

<p>Definition: QOUH represents histological maturity of healed peptic ulcer; Evaluation of QOUH should be done to assess functional and endoscopic maturity additionally to histological maturity; For a clinical use an endoscopic evaluation of maturity should be the main method</p> <p>Criteria: 1: Endoscopic evaluation of maturity Dye-contrast method, magnified endoscopy, endoscopic ultrasonography 2: Histological maturity Regenerated mucosa: thickness, width, morphological abnormalities of glands, inflammatory cell infiltration Granulation tissue: angiogenesis, fibroblasts and fibrosis, regeneration of muscularis mucosae, inflammatory cell infiltration 3: Functional evaluation of maturity Microcirculation, production of mucin, prostanoids, growth factors, cell proliferation, receptor expression, adhesion molecules</p>
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Arakawa *et al*^[12]. QOUH: Quality of ulcer healing.

ogy and life cycle of ulcer recurrence. Tarnawski *et al*^[9] have demonstrated in this rat model that the subepithelial mucosa of macroscopically healed gastric ulcer displays disorganized restoration of glandular and vascular structures and remains histologically and ultrastructurally abnormal. They have concluded that these abnormalities may interfere with oxygenation, nutrient supply, and with mucosal resistance and defense, and therefore could be the basis for ulcer recurrence. They proposed the concept of QOUH based on an experimental ulcer model in 1990^[9-11]. In a previous clinical study by our group, we proposed the concept and definition of QOUH in human gastric ulcer in a Japanese journal, which was published in an English journal 18 mo later^[12] (Table 1). A flat or non-flat ulcer scar pattern has been defined with chromoendoscopy using indigo carmine, which was not demonstrated with conventional endoscopy (Figure 2). These patterns are compatible with histological maturity of regenerated mucosa of healed gastric ulcer; the flat pattern represents a good QOUH and non-flat represents poor QOUH^[13] (Figure 2). The incidence of ulcer recurrence is much higher in a non-flat scar than in a flat scar pattern^[13,14] (Figure 3), suggesting that the endoscopically assessed QOUH may detect scars that are predisposed to future ulcer recurrence.

ULCER HEALING AND PROSTAGLANDINS

Prostaglandins (PGs) and the discovery of the phenomenon of cytoprotection by Robert *et al*^[15] sparked an enormous interest in the critical role of PGs in mucosal defense and ulcer healing. In humans, “artificial” ulcers in the gastrointestinal tract produced by endoscopic mucosal resection for neoplasm heal rapidly and do not recur. We have shown that the surrounding mucosa of such artificial ulcers synthesizes increased amount of prostaglandin E2 (PGE2) and prostacyclin^[16], which may have a crucial role in producing high QOUH. This

observation has led to our contention that PUD may be a PG-deficiency disease^[17] and that PG deficiency may cause poor QOUH. We have demonstrated that low-dose indomethacin causing PG-insufficiency forms an experimental chronic gastric ulcer with poor QOUH, and that exogenous PGE2 reverses poor QOUH as assessed by recurrence rate after healing, and reduces inflammatory cell infiltration of the ulcer scar^[18] (Figure 4). Therefore, PG derivatives and/or PG-inducing drugs such as mucosal protective compounds may promote high QOUH^[19,20].

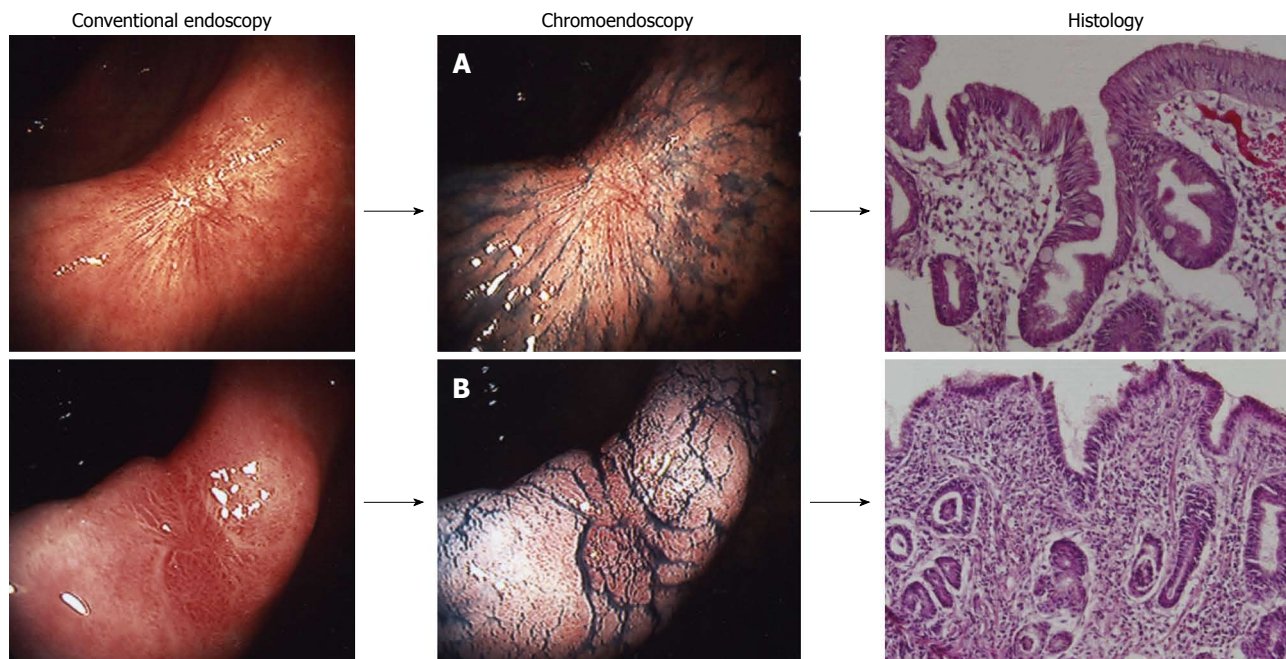
Another important factor in poor QOUH could be a deficiency and/or an imbalance of endogenous growth factors. Jones *et al*^[21] have demonstrated that local gene therapy with vascular endothelial growth factor (VEGF) and angiopoietin 1 (Ang1), with limited duration of target gene expression, significantly accelerates experimental gastric ulcer healing in rats. Co-injection of both plasmids encoding rhVEGF 165 and rhAng1 resulted in formation of more mature vessels and more complete restoration of gastric glandular structures within the ulcer scar, reflecting better QOUH. Inhibition of accelerated healing by a neutralizing anti-VEGF antibody indicates an essential role for VEGF and enhanced angiogenesis in ulcer healing.

PATHOPHYSIOLOGY OF QOUH

Histological evaluation of scars of healed gastric ulcers shows increased infiltration of regenerated tissue with numerous neutrophils and macrophages in a non-flat scar compared to a flat scar (Figure 5). The persistence of chronic inflammation may be reflected by the finding of a hypoechoic area beneath the ulcer scar with a non-flat pattern, assessed by endoscopic ultrasonography (Figure 6). The number of macrophages infiltrating scar tissue is five times higher than neutrophils in a non-flat scar, suggesting that these macrophages may play a key role in pathophysiology of QOUH, and hence future ulcer recurrence. These macrophages produce increased amounts of interleukin (IL)-1 β , tumor necrosis factor (TNF)- α , and monocyte chemotactic protein (MCP)-1 (Figure 7). The proinflammatory cytokines, IL-1 β and TNF- α further activate and stimulate macrophages, thus constituting a self-perpetuating circuit. The increased stimulation of production of these cytokines induced by NSAIDs, stress, or *H. pylori* may cause these macrophages to increase cytokine production and/or release, leading in turn to attraction and accumulation of neutrophils. Neutrophils by releasing proteases and active oxygen species damage the scar tissue and induce ulcer recurrence.

MECHANISMS UNDERLYING ULCER RECURRENCE

As mentioned previously, Okabe's rat model of chronic ulcer mimics human peptic ulcer not only morphologi-



Endoscopic pattern	<i>n</i>	Regenerated gland index	<i>P</i> -value
Flat	10	48.0 ± 2.8	< 0.05
Non-flat	5	40.2 ± 2.6	

Figure 2 Assessment of endoscopic quality of ulcer healing. Flat pattern (A) and non-flat pattern (B) are identified by chromoendoscopy, but not by conventional endoscopy. Flat pattern reflects good quality of healing compared to nodular pattern as assessed by histological maturity (Arakawa *et al*^[12]).

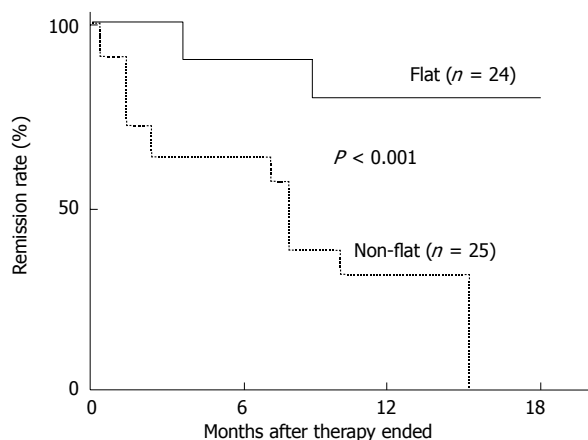


Figure 3 Cumulative remission rates of healed gastric ulcers with flat and non-flat pattern. The incidence of ulcer recurrence is much higher in the ulcer scar with a non-flat than flat pattern (Nebiki *et al*^[14]).

cally and histologically but also with regard to the life cycle of spontaneous recurrence. Numerous neutrophils and macrophages persist in and beneath the regenerated epithelium even after ulcer healing. This persistent chronic inflammation may have a key role in causing future ulcer recurrence. Watanabe *et al*^[22] have demonstrated that inflammatory cytokines, IL-1 β and TNF- α , administered systemically in rats with macroscopically healed gastric ulcer, cause ulcer recurrence at the site of the previous ulcer (Figure 8). In this model of gastric

ulcer recurrence that we reported in 1997, we found increased expression of adhesion molecules, intercellular adhesion molecule (ICAM)-1 in endothelial cells and leukocytic β_2 integrins, lymphocyte function-associated antigen (LFA-1; CD11a/CD18) and Mac-1 (CD11b/CD18) in leukocytes, and also of cytokines, IL1 β and TNF- α ^[22], and chemokine, MCP-1^[23]. This increase occurred in the regenerated tissue of the healed ulcer site (scar) 12 h after injection of an inflammatory cytokine, and was followed by massive infiltration of macrophages and neutrophils, ultimately resulting in ulcer recurrence. Antineutrophil antiserum prevents ulcer recurrence in this model, suggesting that neutrophils (producing noxious protease and active oxygen species) are the final mediator of tissue injury^[22]. This hypothesis is further supported by the demonstration that antibodies against adhesion molecules (ICAM-1 and LFA-1) also inhibit ulcer recurrence^[22]. These molecules regulate migration of neutrophils from arterioles into the interstitial space. Antibody against MCP-1 prevents gastric ulcer recurrence in this model^[23], suggesting that the overexpression of MCP-1 in resident macrophages accumulated in the interstitial space of the ulcer scar is a first step in the mechanism of ulcer recurrence, because neutrophils and macrophages infiltrate the interstitial space of the ulcer scar only after overexpression of MCP-1^[24]. Proton-pump inhibitors (PPIs) prevent gastric ulcer recurrence caused by injection of IL1 β ^[24] and administration of

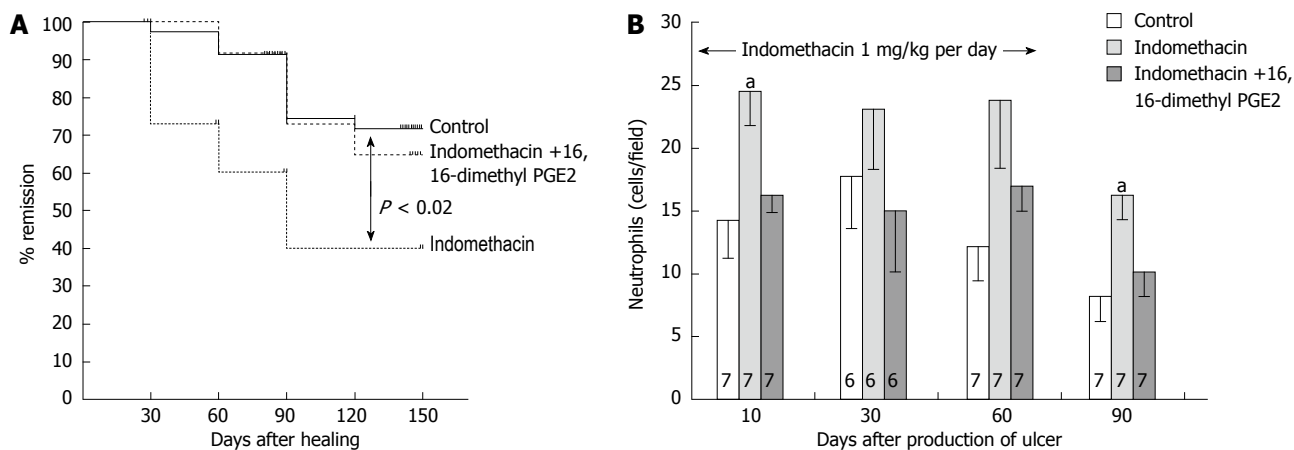


Figure 4 Effect of low-dose indomethacin given during initial period of healing process of gastric ulcer induced by application of acetic acid in rats on cumulative remission rate after healing and on neutrophil infiltration of the interstitial space of the ulcer scar. Indomethacin treatment enhances neutrophil infiltration and this phenomenon persists even after cessation of this drug. Concomitant administration of 16, 16-dimethyl prostaglandin E₂ (PGE₂) with indomethacin reverses these effects by indomethacin. A: Cumulative remission rate after healing; B: Infiltration with polymorphonuclear cells during and after healing. Control; indomethacin; indomethacin + 16, 16-dimethyl prostaglandin E₂ (Arakawa *et al.*^[18]). ^a*P* < 0.05 vs control group.

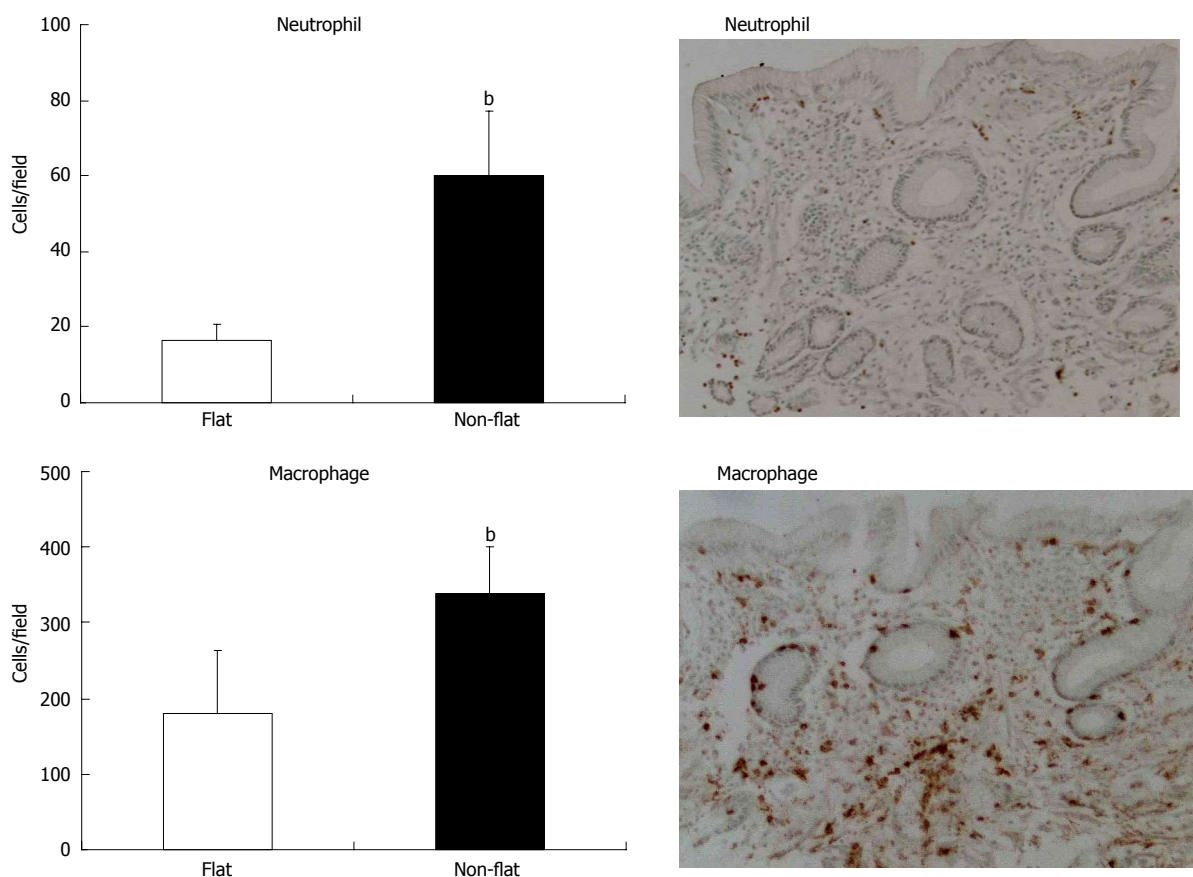
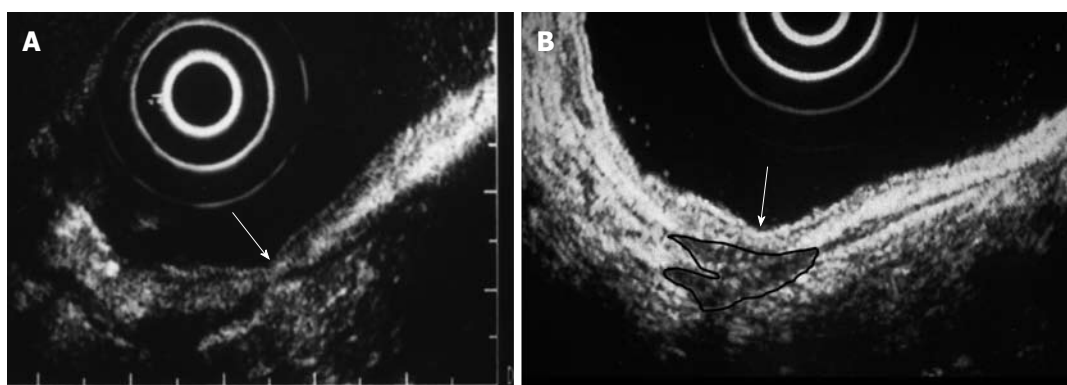


Figure 5 Number of inflammatory cells infiltrating interstitial space of ulcer scar with flat or non-flat pattern assessed by chromoendoscopy in patients with macroscopically healed gastric ulcer. The number of neutrophils and macrophages is much higher in non-flat than in flat pattern. The number of macrophages is increased five times vs neutrophils in non-flat scar. *n* = 6, ^b*P* < 0.01 vs flat group.

exogenous acid reverses the protective action of PPIs on ulcer recurrence, suggesting that presence of acid is necessary to induce ulcer recurrence^[24]. Based on these studies, we propose a working hypothesis of gastric ulcer recurrence presented in Figure 9^[25].

EFFECT OF ANTIULCER DRUGS ON QOUH

The histological maturity of regenerated mucosa is poor after treatment with H₂-receptor antagonists^[26]. This



	Flat	Non-flat	P-value
Internal hypoechoic area (+/-)	3/21	16/9	0.0003

Figure 6 Assessment of interstitial space beneath gastric ulcer scar with endoscopic ultrasonography. Hypoechoic area (circle of black line) is clearly seen in non-flat scar (B), but not in flat scar (A). Arrow shows a point of ulcer scar (Nebiki *et al*^[14]).

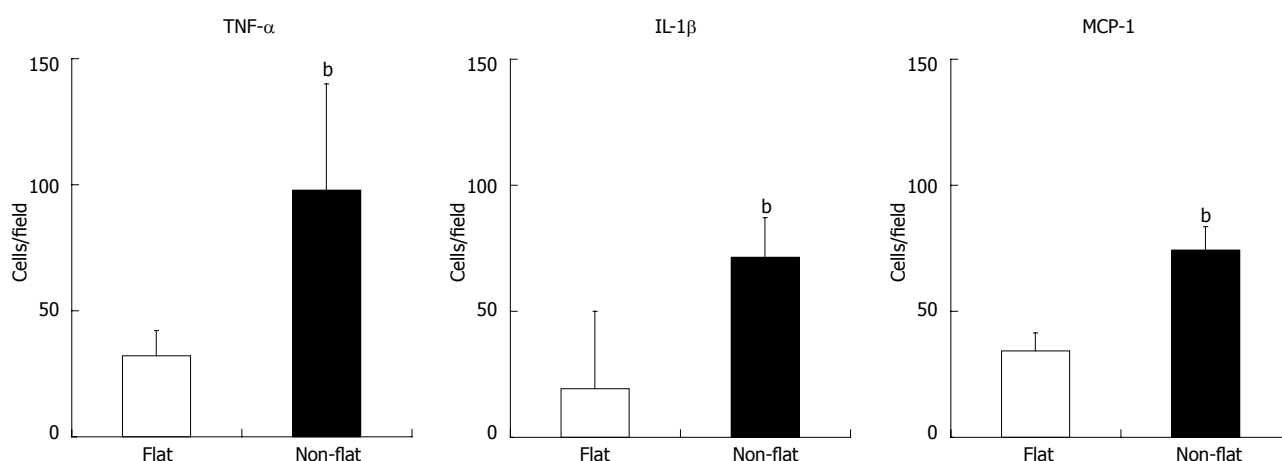


Figure 7 Number of tumor necrosis factor- α -, interleukin-1 β -, and monocyte chemoattractant protein-1-producing cells in interstitial space of ulcer scar site in patients with gastric ulcer whose ulcer healed with flat vs non-flat pattern assessed by chromoendoscopy. $n = 6$, ^b $P < 0.01$ vs flat group. TNF- α : Tumor necrosis factor α ; IL-1 β : Interleukin-1 β ; MCP-1: Monocyte chemoattractant protein-1.

may be related to their action to decrease mucosal PG levels^[27]. Rebamipide, a mucosal-protective drug that stimulates synthesis of PGs, accelerates ulcer healing and reduces relapse of acetic-acid-induced gastric ulcer in rats. In contrast, ulcer relapse is not prevented by cimetidine^[26]. Similar results regarding improving QOUH by rebamipide have been reported by Qi *et al*^[28]. In a clinical setting rebamipide has been shown to improve QOUH of human gastric ulcers, as assessed by chromoendoscopy. Moreover, the ulcer recurrence rate after healing with rebamipide was similar to that found in gastric ulcer patients after *H. pylori* eradication with dual therapy^[29]. Rebamipide has been shown to exert anti-inflammatory action, accelerate gastric ulcer healing, and promote high QOUH in both experimental and clinical studies^[30,31].

Regarding the action of other drugs related to QOUH, antacid hydrotalcite provides better restoration of glandular structures in the gastric ulcer scar in rats

compared to omeprazole^[32]. In clinical studies, initial treatment with sucralfate is superior to cimetidine in decreasing recurrence rate of healed duodenal ulcer during maintenance therapy with cimetidine^[33]. Direct evidence of promoting better QOUH, as assessed by chromoendoscopy, has been reported with lafutidine in a placebo-controlled trial, and ranitidine compared to famotidine in patients with gastric ulcer^[34,35]. Lafutidine is a novel H₂-receptor antagonist developed in Japan. It has the unique property of stimulating capsaicin-sensitive nerves, producing NO, a cytoprotective mediator.

RECENT ADVANCES IN EVALUATION OF QOUH

Recent preliminary findings with magnifying endoscopy and narrow band imaging (NBI) may be useful for a more precise evaluation of QOUH. Magnifying endoscopy shows a fine regular glandular pattern in flat scar

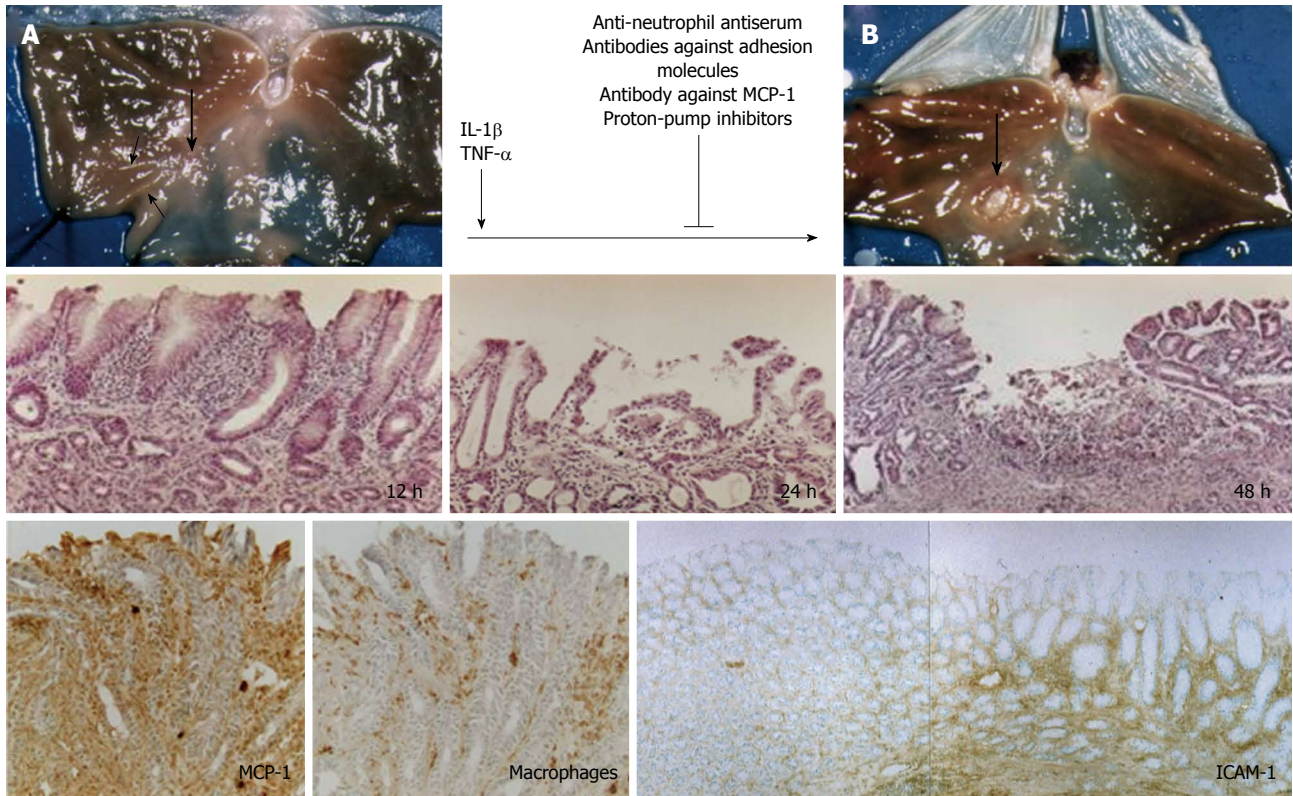


Figure 8 Original rat model of gastric ulcer recurrence. A: Ulcer scar of acetic-acid-induced gastric ulcer healed spontaneously (big arrow) with fold convergence (small arrows); B: Recurrence of ulcer with white coat at the same site as previous ulcer (big arrow). Interleukin-1 β (IL-1 β) or tumor necrosis factor α (TNF- α) administered systemically causes recurrence of ulcer macroscopically and histologically. Antineutrophil antiserum, antibodies against adhesion molecules, antibody against monocyte chemoattractant protein-1 (MCP-1), or proton-pump inhibitors prevent recurrence. MCP-1 is overexpressed in macrophages in the interstitial space of the ulcer scar site at 12 h after administration of IL-1 β or TNF- α . Adhesion molecules are overexpressed only at the ulcer scar site (Watanabe *et al.*^[22-24]). ICAM: Intercellular adhesion molecule.

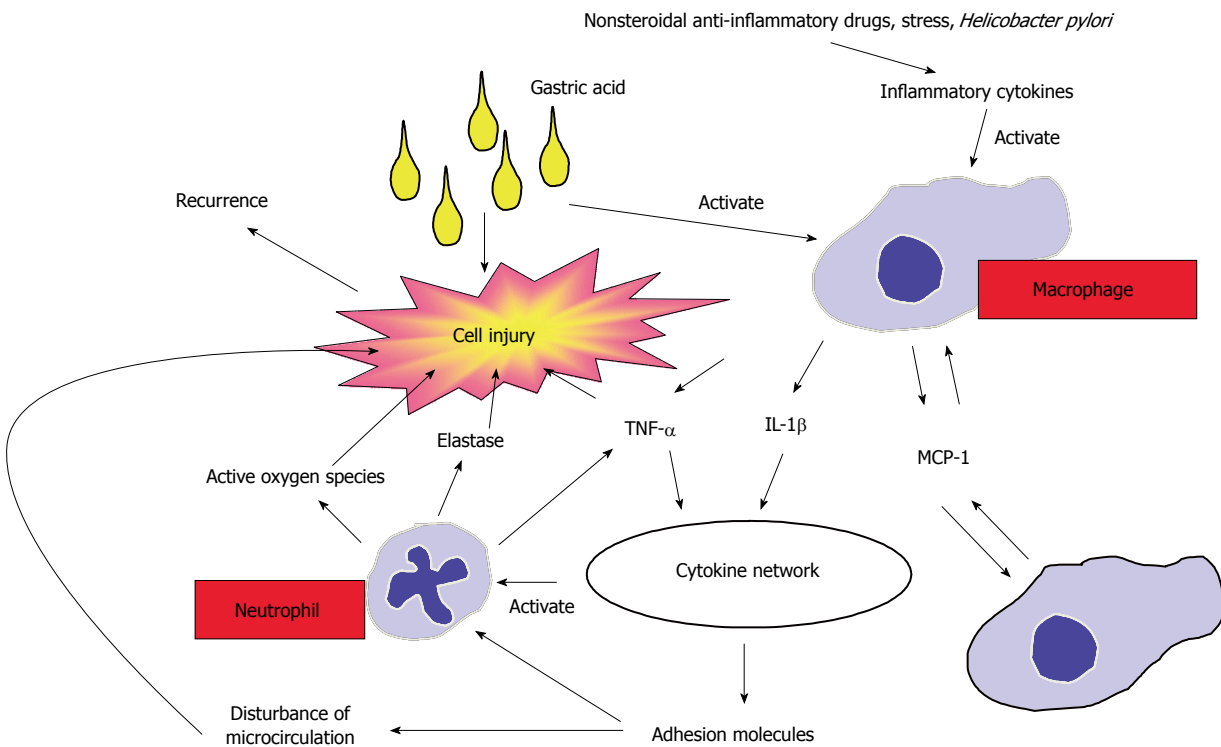


Figure 9 Proposed mechanisms of ulcer recurrence. Ulcerogenic factors such as nonsteroidal anti-inflammatory drugs, stress, and *Helicobacter pylori* stimulate the production of inflammatory cytokines, which activate macrophages under acidic conditions. The activated macrophages produce monocyte chemoattractant protein-1 (MCP-1), which accumulates other macrophages. These macrophages all produce a large amount of interleukin-1 β (IL-1 β) and tumor necrosis factor α (TNF- α), which activate the cytokine network, resulting in activation of adhesion molecules and neutrophils. Activated neutrophils migrate from arterioles to the interstitial space and injure the tissue with noxious substances such as reactive oxygen species and elastase produced by themselves together with gastric acid (Arakawa *et al.*^[25]).

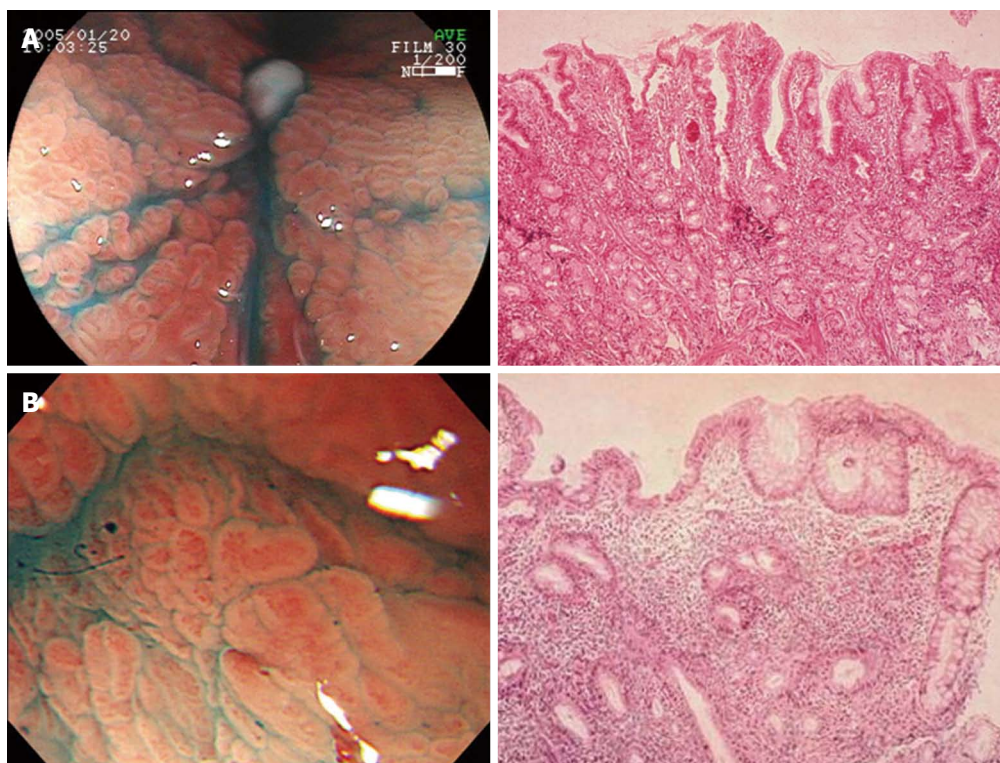


Figure 10 Magnifying chromoendoscopy shows different findings in flat scar as a fine regular pattern (A) and non-flat scar as coarse irregular pattern (B) compatible with histological findings.

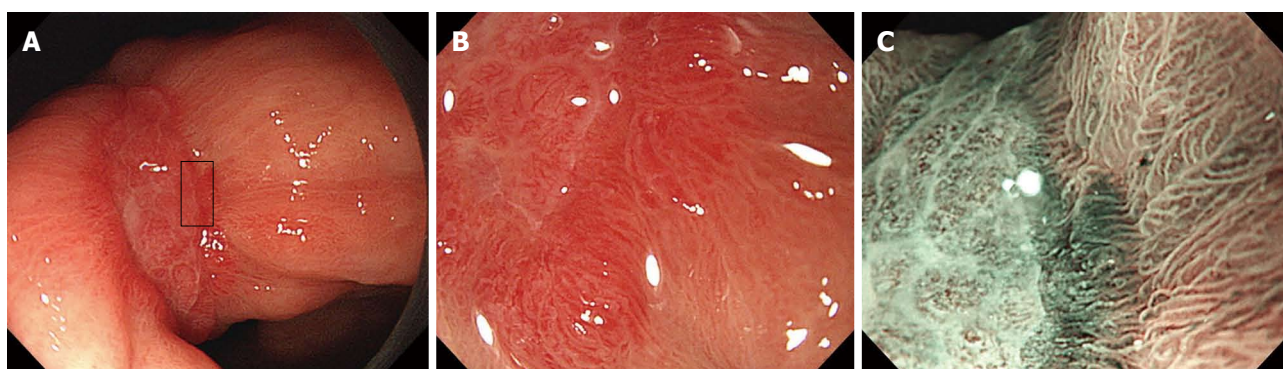


Figure 11 Narrow band imaging with magnification by endoscopy in patients with gastric ulcer shows fine vascular patterns, which may reflect precise quality of ulcer healing. A: Conventional endoscopy; B: Magnifying endoscopy; C: Magnification + narrow band imaging.

and coarse, irregular, and hyperemic glandular pattern in non-flat scar (Figure 10), suggesting that a more precise assessment is possible in the near future. In addition to this procedure, NBI may be the most promising tool to assess QOUH combined with magnification because NBI shows pattern of vessels that may reflect QOUH (Figure 11).

MUCOSAL HEALING IN CROHN'S DISEASE

Biological drugs aimed at TNF- α , such as infliximab (and other related antibodies) as well as thalidomide^[36], promote ulcer healing in Crohn's disease resistant to cor-

ticosteroids. This action is completely different from the mucosal healing obtained with a PPI for gastric and/or duodenal ulcers, because a PPI inhibits only acid secretion, but may not suppress inflammation. Therefore, PPIs promote rapid healing of acid-related ulcers, but do not improve QOUH, especially in the presence of *H. pylori*. The biological drugs directly suppress inflammation, and thus they may improve QOUH. However, as long as the factor responsible for inflammation is unknown, the efficacy of such drugs may be limited.

Granulomas beneath the regenerated tissue may have an important role in cell-to-cell contact of macrophages with T lymphocytes in Crohn's disease and cause chronic inflammation, and on this background poor QOUH^[37,38].

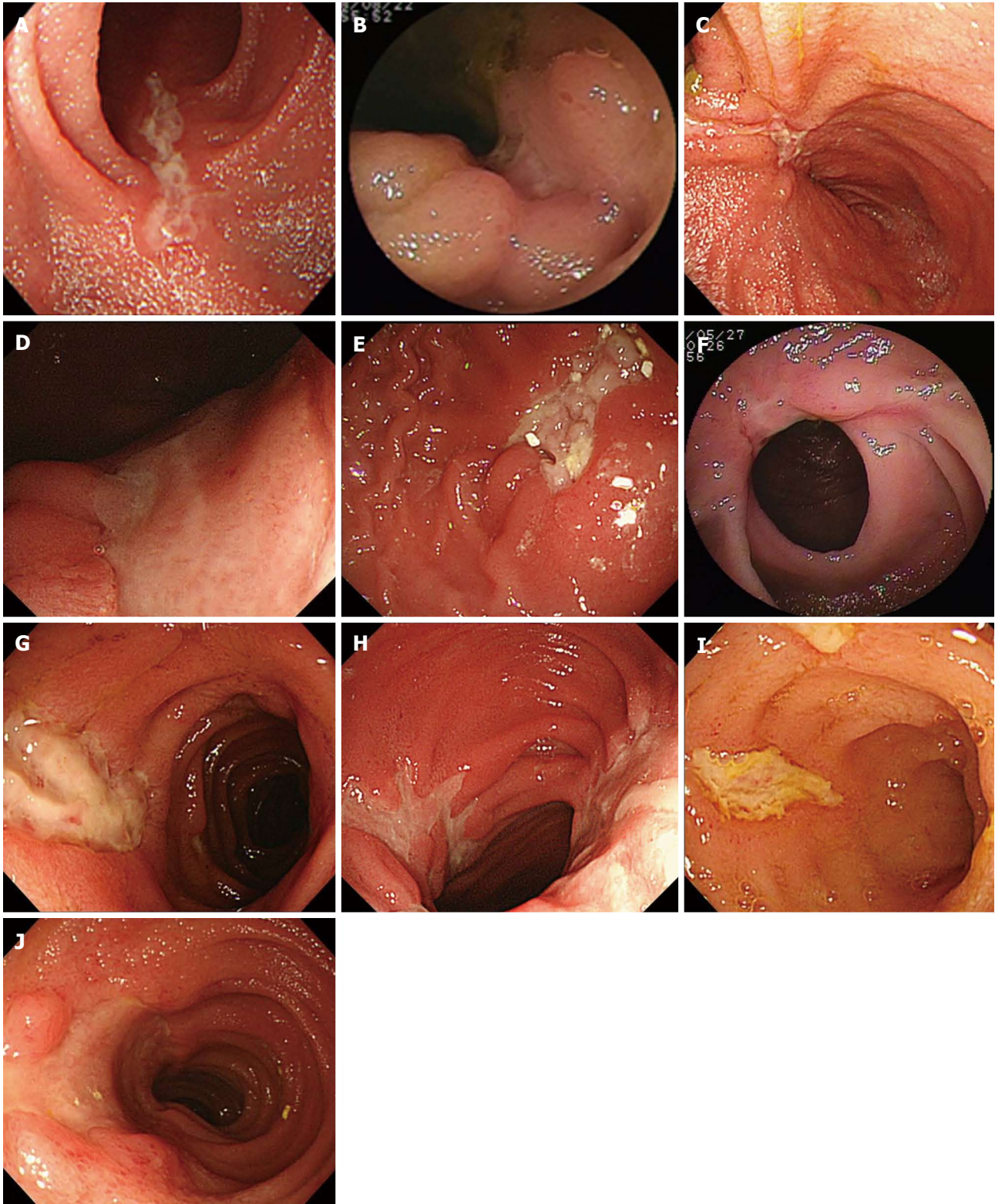


Figure 12 Morphological characteristics of active ulcer in patients with Crohn's disease. Shape of ulcer edge, flat (A) or non-flat (B); fold convergence, negative or positive (C); shape of ulcer base, flat (D) or non-flat (E); stenosis, negative or positive (F); neighboring ulcer, negative (G) or positive (H); width of ulcer, narrow (I) or wide (J).

The inflammation in Crohn's disease is based on Th1 and Th17 reaction^[39-41] that is similar to *H. pylori*-associated gastritis^[42,43]. Therefore, the inflammation in Crohn's disease may have similar immunopathophysiology to

H. pylori-associated inflammation, which causes poor QOUH and underlies the ulcer recurrence. The similarity of immunological abnormality in Crohn's disease and *H. pylori*-associated gastritis may also be related to distur-

Table 2 Morphological characteristics of active ulcers in patients with Crohn's disease reflecting possible future mucosal healing after treatment with infliximab

Morphological finding	Mucosal healing			P value ¹
	Good (n = 10)	Poor (n = 11)		
Shape of ulcer edge	Flat	8	3	0.03
	Non-flat	2	8	
Fold convergence	Negative	7	3	0.08
	Positive	3	8	
Shape of ulcer base	Flat	4	3	0.65
	Non-flat	6	8	
Stenosis	Negative	8	9	0.99
	Positive	2	2	
Neighboring ulcer	Negative	9	4	0.02
	Positive	1	7	
Width of ulcer	Narrow	9	4	0.02
	Wide	1	7	

¹Fisher's exact test. P value indicates the statistical difference in morphological findings between good and poor mucosal healing.

bance of the ghrelin system^[44,45].

In our preliminary study of 21 patients with Crohn's disease treated with infliximab, morphological characteristics of active ulcer were defined, namely shape of ulcer edge, flat or non-flat; fold convergence, negative or positive; shape of ulcer base, flat or non-flat; stenosis, negative or positive; neighboring ulcer, negative or positive; width of ulcer, narrow or wide (Figure 12). The incidence of mucosal healing of active ulcer with a flat edge, absence of neighboring ulcer, or a narrow width of ulcer is significantly higher. A negative mucosal fold convergence tends to be more frequent than non-flat ulcer edge, positive fold convergence, positive neighboring ulcer, or wide ulcer (Table 2). The latter type of ulcer may require stronger anti-inflammatory treatment to obtain mucosal healing. These ulcers may need an endoscopic follow-up observation with assessment of mucosal healing after remission. If the ulcer does not recur, the mucosal healing may be high QOUH. Mucosal fold convergence (Figure 12C) may be one of the factors reflecting poor QOUH. Therefore, prevention of the convergence may improve QOUH of Crohn's disease. Stimulation of the local angiotensin II system may have a key role in fibrosis, resulting in fold convergence and stricture^[46], suggesting that inhibitors on this system such as angiotensin II receptor blockers may promote high QOUH in Crohn's disease. However, to identify a causative factor of inflammation in Crohn's disease is the most essential. The responsible antigen needs to be elucidated from candidates such as yeast-like antigen^[47], and others. Elimination of the possible antigen may be a powerful tool to obtain high QOUH and permanent remission.

The concept and the paradigm of QOUH may also apply to ulcerative colitis. Tarnawski and coworkers using confocal endomicroscopy and molecular imaging have demonstrated in colonic mucosa of patients with

ulcerative colitis in remission impaired crypt regeneration, persistent inflammation, pathological angiogenesis and increased microvascular permeability; all reflecting impaired QOUH. They have found that the underlying mechanisms include dysregulation of survivin, aberrant activation of VEGF gene, and persistent inflammatory cell infiltration^[48].

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REFERENCES

- 1 Arakawa T, Higuchi K, Fujiwara Y, Tominaga K, Watanabe T, Shiba M, Uchida T, Kuroki T. Helicobacter pylori: criminal or innocent bystander? *J Gastroenterol* 2000; **35** Suppl 12: 42-46
- 2 Jang HJ, Choi MH, Shin WG, Kim KH, Chung YW, Kim KO, Park CH, Baek IH, Baik KH, Kae SH, Kim HY. Has peptic ulcer disease changed during the past ten years in Korea? A prospective multi-center study. *Dig Dis Sci* 2008; **53**: 1527-1531
- 3 Musumba C, Jorgensen A, Sutton L, Van Eker D, Moorcroft J, Hopkins M, Pritchard DM, Pirmohamed M. The relative contribution of NSAIDs and Helicobacter pylori to the aetiology of endoscopically-diagnosed peptic ulcer disease: observations from a tertiary referral hospital in the UK between 2005 and 2010. *Aliment Pharmacol Ther* 2012; **36**: 48-56
- 4 Sbrozzi-Vanni A, Zullo A, Di Giulio E, Hassan C, Corleto VD, Lahner E, Annibale B. Low prevalence of idiopathic peptic ulcer disease: an Italian endoscopic survey. *Dig Liver Dis* 2010; **42**: 773-776
- 5 Kang JM, Seo PJ, Kim N, Lee BH, Kwon J, Lee DH, Jung HC. Analysis of direct medical care costs of peptic ulcer disease in a Korean tertiary medical center. *Scand J Gastroenterol* 2012; **47**: 36-42
- 6 Oi M, Oshida K, Sugimura S. The location of gastric ulcer. *Gastroenterology* 1959; **36**: 45-56
- 7 Pan S, Liao CH. The histological maturity of regenerating mucosa of healed duodenal ulcer and ulcer recurrence after treatment with H2-antagonist. *Am J Gastroenterol* 1990; **85**: 949-952
- 8 Takagi K, Okabe S, Saziki R. A new method for the production of chronic gastric ulcer in rats and the effect of several drugs on its healing. *Jpn J Pharmacol* 1969; **19**: 418-426
- 9 Tarnawski A, Hollander D, Krause WJ, Dabros W, Stachura J, Gergely H. "Healed" experimental gastric ulcers remain histologically and ultrastructurally abnormal. *J Clin Gastroenterol* 1990; **12** Suppl 1: S139-S147
- 10 Tarnawski A, Douglass TG, Stachura J, Krause WJ. Quality of gastric ulcer healing: histological and ultrastructural assessment. *Aliment Pharmacol Ther* 1991; **5** Suppl 1: 79-90
- 11 Tarnawski A, Stachura J, Krause WJ, Douglass TG, Gergely H. Quality of gastric ulcer healing: a new, emerging concept. *J Clin Gastroenterol* 1991; **13** Suppl 1: S42-S47
- 12 Arakawa T, Kobayashi K. Quality of ulcer healing--a new concept to rank healed peptic ulcers. *Gastroenterol Jpn* 1993; **28** Suppl 5: 158-162
- 13 Arakawa T, Nebiki H, Uchida T, Kimura S, Higuchi K, Kobayashi K. Clinical assessment of quality of ulcer healing-a

- new approach of endoscopic evaluation. *Eur J Gastroenterol Hepatol* 1993; **5** Suppl 3: S87-S92
- 14 **Nebiki H**, Arakawa T, Higuchi K, Kobayashi K. Quality of ulcer healing influences the relapse of gastric ulcers in humans. *J Gastroenterol Hepatol* 1997; **12**: 109-114
 - 15 **Robert A**, Nezamis JE, Lancaster C, Hanchar AJ. Cytoprotection by prostaglandins in rats. Prevention of gastric necrosis produced by alcohol, HCl, NaOH, hypertonic NaCl, and thermal injury. *Gastroenterology* 1979; **77**: 433-443
 - 16 **Kobayashi K**, Arakawa T, Nakamura H, Chono S, Yamada H, Satoh H, Kamata T, Ono T. Protective action of endogenous prostacyclin (PGI₂) and prostaglandin E₂ (PGE₂) in endoscopic polypectomy-induced human ulcers. *Gastroenterol Jpn* 1982; **17**: 430-433
 - 17 **Kobayashi K**, Arakawa T, Nakamura H, Chono S, Yamada H, Kamata T, Ono T. Role of prostaglandin E₂ on human gastric ulcers. *Gastroenterol Jpn* 1982; **17**: 21-24
 - 18 **Arakawa T**, Watanabe T, Fukuda T, Higuchi K, Takaishi O, Yamasaki K, Kobayashi K, Tarnawski A. Indomethacin treatment during initial period of acetic acid-induced rat gastric ulcer healing promotes persistent polymorphonuclear cell-infiltration and increases future ulcer recurrence. Possible mediation of prostaglandins. *Dig Dis Sci* 1996; **41**: 2055-2061
 - 19 **Kobayashi K**, Arakawa T. Arachidonic acid cascade and gastric mucosal injury, protection, and healing: topics of this decade. *J Clin Gastroenterol* 1995; **21** Suppl 1: S12-S17
 - 20 **Arakawa T**, Higuchi K, Fukuda T, Fujiwara Y, Kobayashi K, Kuroki T. Prostaglandins in the stomach: an update. *J Clin Gastroenterol* 1998; **27** Suppl 1: S1-11
 - 21 **Jones MK**, Kawanaka H, Baatar D, Szabó IL, Tsugawa K, Pai R, Koh GY, Kim I, Sarfeh IJ, Tarnawski AS. Gene therapy for gastric ulcers with single local injection of naked DNA encoding VEGF and angiopoietin-1. *Gastroenterology* 2001; **121**: 1040-1047
 - 22 **Watanabe T**, Arakawa T, Fukuda T, Higuchi K, Kobayashi K. Role of neutrophils in a rat model of gastric ulcer recurrence caused by interleukin-1 beta. *Am J Pathol* 1997; **150**: 971-979
 - 23 **Watanabe T**, Higuchi K, Hamaguchi M, Shiba M, Tominaga K, Fujiwara Y, Matsumoto T, Arakawa T. Monocyte chemoattractant protein-1 regulates leukocyte recruitment during gastric ulcer recurrence induced by tumor necrosis factor- α . *Am J Physiol Gastrointest Liver Physiol* 2004; **287**: G919-G928
 - 24 **Watanabe T**, Higuchi K, Tominaga K, Fujiwara Y, Arakawa T. Acid regulates inflammatory response in a rat model of induction of gastric ulcer recurrence by interleukin 1beta. *Gut* 2001; **48**: 774-781
 - 25 **Arakawa T**, Watanabe T, Fukuda T, Higuchi K, Fujiwara Y, Kobayashi K, Tarnawski A. Ulcer recurrence: cytokines and inflammatory response-dependent process. *Dig Dis Sci* 1998; **43**: 61S-66S
 - 26 **Arakawa T**, Watanabe T, Fukuda T, Yamasaki K, Kobayashi K. Rebamipide, novel prostaglandin-inducer accelerates healing and reduces relapse of acetic acid-induced rat gastric ulcer. Comparison with cimetidine. *Dig Dis Sci* 1995; **40**: 2469-2472
 - 27 **Arakawa T**, Satoh H, Fukuda T, Sakuma H, Nakamura H, Kobayashi K. Gastric mucosal resistance and prostanoid levels after cimetidine treatment in rats. *Digestion* 1988; **41**: 1-8
 - 28 **Qi Z**, Jie L, Haixia C, Xiaoying Z. Effect of rebamipide on quality of peptic ulcer healing in rat. *Dig Dis Sci* 2009; **54**: 1876-1883
 - 29 **Higuchi K**, Arakawa T, Nebiki H, Uchida T, Fujiwara Y, Ando K, Yamasaki K, Takaishi O, Fukuda T, Kobayashi K, Kuroki T. Rebamipide prevents recurrence of gastric ulcers without affecting Helicobacter pylori status. *Dig Dis Sci* 1998; **43**: 99S-106S
 - 30 **Arakawa T**, Kobayashi K, Yoshikawa T, Tarnawski A. Rebamipide: overview of its mechanisms of action and efficacy in mucosal protection and ulcer healing. *Dig Dis Sci* 1998; **43**: 5S-13S
 - 31 **Arakawa T**, Higuchi K, Fujiwara Y, Watanabe T, Tominaga K, Sasaki E, Oshitani N, Yoshikawa T, Tarnawski AS. 15th anniversary of rebamipide: looking ahead to the new mechanisms and new applications. *Dig Dis Sci* 2005; **50** Suppl 1: S3-S11
 - 32 **Schmassmann A**, Tarnawski A, Gerber HA, Flogerzi B, Sanner M, Varga L, Halter F. Antacid provides better restoration of glandular structures within the gastric ulcer scar than omeprazole. *Gut* 1994; **35**: 896-904
 - 33 **Tovey FI**, Husband EM, Yiu YC, Baker L, McPhail G, Jayaraj AP, Lewin MR, Clark CG. Differences in mucosal appearances and in relapse rates in duodenal ulceration treated with sucralfate or cimetidine. *Am J Med* 1989; **86**: 141-144
 - 34 **Higuchi K**, Watanabe T, Tominaga K, Shiba M, Nakagawa K, Uno H, Kitada K, Satoh H, Chono S, Oshitani N, Fujiwara Y, Arakawa T. Lafutidine can improve the quality of gastric ulcer healing in humans: a randomized, controlled, multicenter trial. *Inflammopharmacology* 2006; **14**: 226-230
 - 35 **Higuchi K**, Watanabe T, Tominaga K, Shiba M, Nakagawa K, Uno H, Kitada K, Satoh H, Chono S, Uchida T, Fujiwara Y, Arakawa T. Effects of ranitidine on quality of gastric ulcer healing compared with famotidine: a randomized, controlled, multicenter trial. *Int J Clin Pharmacol Res* 2005; **25**: 187-194
 - 36 **Leite MR**, Santos SS, Lyra AC, Mota J, Santana GO. Thalidomide induces mucosal healing in Crohn's disease: case report. *World J Gastroenterol* 2011; **17**: 5028-5031
 - 37 **Hara J**, Ohtani H, Matsumoto T, Nakamura S, Kitano A, Arakawa T, Nagura H, Kobayashi K. Expression of costimulatory molecules B7-1 and B7-2 in macrophages and granulomas of Crohn's disease: demonstration of cell-to-cell contact with T lymphocytes. *Lab Invest* 1997; **77**: 175-184
 - 38 **Kakazu T**, Hara J, Matsumoto T, Nakamura S, Oshitani N, Arakawa T, Kitano A, Nakatani K, Kinjo F, Kuroki T. Type 1 T-helper cell predominance in granulomas of Crohn's disease. *Am J Gastroenterol* 1999; **94**: 2149-2155
 - 39 **Morimoto K**, Hosomi S, Yamagami H, Watanabe K, Kamata N, Sogawa M, Machida H, Okazaki H, Tanigawa T, Nagahara H, Noda E, Tominaga K, Watanabe T, Fujiwara Y, Maeda K, Hirakawa K, Arakawa T. Dysregulated upregulation of T-cell immunoglobulin and mucin domain-3 on mucosal T helper 1 cells in patients with Crohn's disease. *Scand J Gastroenterol* 2011; **46**: 701-709
 - 40 **Kawashima D**, Oshitani N, Jinno Y, Watanabe K, Nakamura S, Higuchi K, Arakawa T. Augmented expression of secondary lymphoid tissue chemokine and EB1 ligand chemokine in Crohn's disease. *J Clin Pathol* 2005; **58**: 1057-1063
 - 41 **Monteleone I**, Sarra M, Pallone F, Monteleone G. Th17-related cytokines in inflammatory bowel diseases: friends or foes? *Curr Mol Med* 2012; **12**: 592-597
 - 42 **Hitzler I**, Kohler E, Engler DB, Yazgan AS, Müller A. The role of Th cell subsets in the control of Helicobacter infections and in T cell-driven gastric immunopathology. *Front Immunol* 2012; **3**: 142
 - 43 **Otani K**, Watanabe T, Tanigawa T, Okazaki H, Yamagami H, Watanabe K, Tominaga K, Fujiwara Y, Oshitani N, Arakawa T. Anti-inflammatory effects of IL-17A on Helicobacter pylori-induced gastritis. *Biochem Biophys Res Commun* 2009; **382**: 252-258
 - 44 **Hosomi S**, Oshitani N, Kamata N, Sogawa M, Yamagami H, Watanabe K, Tominaga K, Watanabe T, Fujiwara Y, Maeda K, Hirakawa K, Arakawa T. Phenotypical and functional

- study of ghrelin and its receptor in the pathogenesis of Crohn's disease. *Inflamm Bowel Dis* 2008; **14**: 1205-1213
- 45 **Ochi M**, Tominaga K, Tanaka F, Tanigawa T, Shiba M, Watanabe T, Fujiwara Y, Oshitani N, Higuchi K, Arakawa T. Effect of chronic stress on gastric emptying and plasma ghrelin levels in rats. *Life Sci* 2008; **82**: 862-868
- 46 **Suekane T**, Ikura Y, Watanabe K, Arimoto J, Iwasa Y, Sugama Y, Kayo S, Sugioka K, Naruko T, Maeda K, Hirakawa K, Arakawa T, Ueda M. Phenotypic change and accumulation of smooth muscle cells in strictures in Crohn's disease: relevance to local angiotensin II system. *J Gastroenterol* 2010; **45**: 821-830
- 47 **Oshitani N**, Hato F, Suzuki K, Sawa Y, Matsumoto T, Maeda K, Higuchi K, Kitagawa S, Arakawa T. Cross-reactivity of yeast antigens in human colon and peripheral leukocytes. *J Pathol* 2003; **199**: 361-367
- 48 **Tarnawski AS**, Coron E, Sandor Z, Mosnier JF, Ahluwalia A, Rhun ML, Galmiche JP, Matysiak-Budnik T. Confocal endomicroscopy and molecular imaging demonstrates in colonic mucosa of patients with IBD in remission impaired crypt regeneration, persistent inflammation and pathological angiogenesis. Underlying mechanisms include dysregulation of survivin and aberrant activation of VEGF gene. *Gastroenterology* 2010; **138** Suppl 1: S-75

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