Kari Toljamo

GAstric erosions – Clinical significance and pathology
A Long-term follow-up study
KARI TOLJAMO

GASTRIC EROSIONS – CLINICAL SIGNIFICANCE AND PATHOLOGY
A long-term follow-up study

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in Auditorium 7 of Oulu University Hospital, on 25 May 2012, at 12 noon

UNIVERSITY OF OULU, OULU 2012
Gastric erosions are superficial mucosal breaks. With the exception of bleeding, they are considered harmless, but their aetiology, histopathology and long-term course have remained unknown and even the evolution of gastritis in patients with gastric erosions is unclear. The present study aimed to solve clinical significance and pathology of gastric erosions in a long-term follow-up study.

Initially, 117 patients and 117 controls were studied in 1974–1981, and a follow-up study was performed in 1996. We evaluated the presence of *Helicobacter pylori* and Herpes simplex virus (HSV) infections, use of NSAIDs and alcohol, smoking, and assessed features of gastric histopathology. For follow-up, 52 patients and 66 controls were available.

In the follow-up visit, 39% patients still had gastric erosions while 11% of the controls had developed erosions ($p = 0.001$). In *H. pylori*-positive subjects, peptic ulcer or a scar was more common in patients (17%) than in controls (4%, $p = 0.006$), but otherwise no increased morbidity or mortality was seen. High antibody titres against HSV predicted the persistence of erosions ($p = 0.000$), but *H. pylori* infection, use of NSAIDs, alcohol or smoking were not associated. Initially, inflammation was more active in the region of erosions than elsewhere in the antral mucosa, and more active inflammation in the erosion was associated with HSV seropositivity, *H. pylori* infection and the recent use of NSAIDs. In *H. pylori*-positive subjects with chronic or recurrent erosions had higher scores of neutrophils compared to those with non-chronic/non-recurrent erosions. In *H. pylori*-positive subjects, body gastritis was initially less active in the patient group. With time, antral gastritis worsened only in the patient group. In *H. pylori*-negative subjects, there was no evolution of gastritis.

These results show that a significant proportion of gastric erosions are chronic/recurrent but mostly without serious complications. However, *H. pylori*-positive patients have a significant risk to develop a peptic ulcer. A significant proportion of chronic gastric erosions is related to HSV infection. Focally enhanced inflammation modified by HSV or NSAID may be important in the pathogenesis of gastric antral erosions. Active inflammation in the erosions seems to predict their chronicity/recurrency. Patients with erosions share the characteristics of gastritis of the duodenal ulcer phenotype.

**Keywords:** follow-up studies, gastric mucosal erosion, gastritis, *H. pylori*, Herpes simplex virus, NSAID, peptic ulcer


Asiasanat: helikobakteeri, Herpes simplex virus, mahalaukun eroosiot, mahalaukun limakalvon tulehdus, NSAID, seurantatutkimukset
To Anja, Pirkka and Samu
Acknowledgements

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I wish to express my deepest gratitude to my supervisors, Docent Seppo Niemelä, M.D., Ph.D., and Professor Tuomo Karttunen, M.D., Ph.D. It was Seppo who proposed this topic for my thesis. He has kindly guided me innumerable times during these years, or actually decades. His expertise in gastroenterology has been invaluable in providing a critical view on how to fit our observations into the more recent scientific literature. Tuomo re-examined all histological samples from both visits. He also has always arranged time to discuss with me problems that I have encountered – and I have encountered many. He has an inexhaustible supply of theories to explain the observations made during the study; these theories were invariably based on the most up-to-date scientific literature about the topic. Seppo and Tuomo formed a pleasant and very balanced supervisory team.

I want to express my gratitude to Professor Juhani Lehtola, M.D., Ph.D., for participating in this study by performing so many of the endoscopies during both visits. Juhani was the Head of the Unit of Gastroenterology during my subspecialization in gastroenterology, and he is one of the most warm-hearted colleagues I ever have met.

I am grateful to co-author Docent Anna-Liisa Karvonen, M.D., Ph.D., who completed her dissertation “Gastric mucosal erosions in elective gastroscopic patients” in 1983, and the subjects in the initial visit of my thesis consist of her study subjects. Anna-Liisa reviewed the erosion classifications of the initial visit findings in addition to co-authoring our publications. I am also grateful to co-author Docent Riitta Karttunen, M.D., Ph.D., who participated in the work with the Herpes simplex virus antibodies. I acknowledge the help of co-author Heli Piiparinen, Ph.D., who participated in our study concerning detection of Herpes simplex virus of histological samples; In this respect, I also wish to thank to Docent Irmeli Lautenschlager, M.D., Ph.D.

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I express my warm gratitude to my parents Karin and Onni for “everything”.

Finally, I want to express my warmest gratitude to my wife Anja and my children Pirkka and Samu for their patience and support during this long process of dissertation – not forgetting the times of absence of home life, during which my loveable mother-in-law, Tora, provided invaluable help to my family.

Oulu March 23th 2012 Kari Toljamo
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>Acetylsalicylic Acid</td>
</tr>
<tr>
<td>CagA</td>
<td>cytotoxin associated gene A</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DNA</td>
<td>deoxyribonucleic acid</td>
</tr>
<tr>
<td><em>H. pylori</em></td>
<td><em>Helicobacter pylori</em></td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>MALToma</td>
<td>mucosa-associated lymphoid tissue lymphoma</td>
</tr>
<tr>
<td>NSAID</td>
<td>non-steroidal anti-inflammatory drug</td>
</tr>
<tr>
<td>PCR</td>
<td>polymerase chain reaction</td>
</tr>
<tr>
<td>TNF</td>
<td>tumour necrosis factor</td>
</tr>
<tr>
<td>( \chi^2 ) test</td>
<td>chi-square test</td>
</tr>
<tr>
<td>UACL</td>
<td>ulcer associated cell lineage</td>
</tr>
</tbody>
</table>
List of original publications

This thesis is based on the following publications, which are referred to in the text by their Roman numerals:


Contents

Abstract .............................. 19
Tiivistelmä ..................................... 21
Acknowledgements ................................ 23
Abbreviations ............................... 24
List of original publications .......... 26
Contents ..................................... 27
1 Introduction .................................. 29
2 Review of the literature ............... 31
   2.1 Orientating figures to the topic .................................. 32
   2.2 Definition of gastric erosion ................................. 33
   2.3 Classification ................................................. 35
       2.3.1 Endoscopic classification of gastric erosions ........ 36
       2.3.2 Acute and chronic erosions ............................. 38
   2.4 Incidence and prevalence of gastric erosions ............... 40
       2.4.1 Prevalence of erosions in asymptomatic subjects .... 41
       2.4.2 Prevalence in clinical series ............................ 42
   2.5 Aetiology of gastric erosions .................................. 44
       2.5.1 Herpes simplex virus ..................................... 45
       2.5.2 Helicobacter pylori ......................................... 47
       2.5.3 Non-steroidal anti-inflammatory drug .................. 49
       2.5.4 Gastric acid ................................................. 50
       2.5.5 Other factors ............................................. 51
       2.5.6 Factors affecting chronicity .............................. 53
   2.6 Pathogenesis of gastric erosions ............................. 55
   2.7 Histopathology of gastric erosions ............................ 57
   2.8 Gastritis in patients with erosion ............................. 59
       2.8.1 Definition of gastritis and classification ............... 60
       2.8.2 Phenotypes and dynamics of gastritis .................. 62
       2.8.3 Gastritis in erosion patients ............................. 63
       2.8.4 Dynamics of gastritis in erosion patients ............... 63
   2.9 Follow-up studies in gastric erosion ......................... 65
   2.10 Clinical significance of gastric erosions ..................... 67
       2.10.1 Symptoms ............................................... 68
       2.10.2 Bleeding ................................................. 69
       2.10.3 Ulcer risk ............................................. 70
2.10.4 Malignancy ................................................................. 38

3 Aims of the study ............................................................ 39

4 Materials and Methods .................................................. 41
  4.1 Patients .............................................................................. 41
  4.2 Controls ............................................................................ 41
  4.3 Endoscopy and biopsies .................................................. 41
  4.4 Histological assessment of gastritis ................................... 42
  4.5 Evaluation of Helicobacter pylori infection and Herpes simplex virus infection ........................................... 43
  4.6 Symptoms and other clinical data .................................... 43
  4.7 Blood chemistry ............................................................. 44
  4.8 Occurrence of Malignancies, Mortality and Causes of Death .................................................. 44
  4.9 Statistical analysis ........................................................ 44
  4.10 Ethical consideration ................................................... 45

5 Results ............................................................................. 47
  5.1 Final study groups ......................................................... 47
  5.2 Types of erosion ........................................................... 50
  5.3 Etiological factors (I) ........................................................ 50
    5.3.1 Herpes simplex virus .................................................. 50
    5.3.2 Helicobacter pylori ....................................................... 51
    5.3.3 Non-steroidal anti-inflammatory drug ......................... 52
    5.3.4 Simultaneous effects of Herpes simplex virus, Helicobacter pylori and non-steroidal anti-inflammatory drug ................................................................. 53
    5.3.5 Other factors and the erosion rate ................................ 54
  5.4 Histopathology of gastric antral erosions (II) ..................... 54
    5.4.1 Comparison of inflammatory changes in the erosion and in the background antral mucosa ................................................................. 54
    5.4.2 Role of Helicobacter pylori on histopathology of erosions ........ 57
    5.4.3 Role of non-steroidal anti-inflammatory drugs on the histopathology of erosions ................................................................. 57
    5.4.4 Role of Herpes simplex seropositivity on the histopathology of erosions ................................................................. 58
    5.4.5 Relationship of histopathological features in erosions and the chronicity/recurrence of the erosions ................................................................. 59
    5.4.6 Histopathological features in erosions and the risk for the development of peptic ulcer or gastric malignancy ................................................................. 59
5.5 Progression of gastritis in patients with gastric erosions (III) ................. 60
  5.5.1 Severity of chronic gastritis ....................................................... 61
  5.5.2 Activity of gastritis ................................................................. 62
  5.5.3 Atrophic changes, intestinal metaplasia and dysplasia ................. 63
  5.5.4 Microscopic erosions and epithelial reactive changes ................. 64
  5.5.5 Non-steroidal anti-inflammatory drug use and features of gastritis ................................................................. 65
  5.5.6 Parietal cell antibodies .............................................................. 66
  5.5.7 Ulcer development during the follow-up .................................... 66
5.6 Clinical features, ulcer and malignancy ........................................... 66
  5.6.1 Endoscopical findings ............................................................. 66
  5.6.2 Symptoms and other clinical data .......................................... 66
  5.6.3 Surgical operations and other diseases .................................... 67
  5.6.4 Occurrence of malignancies, mortality, and causes of death ................................................................. 68
6 Discussion 69
  6.1 Methodological aspects ............................................................... 69
  6.2 Aetiology and pathogenesis of chronic/recurrent gastric erosions .... 70
  6.3 Histopathology of chronic/recurrent gastric erosions .................. 73
  6.4 Progression of gastritis in patients with chronic or recurrent gastric erosions ................................................................. 74
  6.5 Clinical outcome of patients with gastric erosion ......................... 77
  6.6 Future aspects ............................................................................. 79
7 Conclusions 81
References 83
Original publications 93
1 Introduction

Gastric erosions have been defined as endoscopically detectable mucosal breaks that do not penetrate the muscularis mucosae (Yardley & Hendrix 1995). The duration of erosion can be short-term, chronic or recurrent (Karvonen & Lehtola 1984, Yardley & Hendrix 1995). Erosions are a frequent finding in 3–12% asymptomatic volunteers and in 4–49% of clinical series (Tables 2 and 3).

The aetiology of gastric erosions of indeterminate duration has been postulated to involve Herpes simplex virus (HSV), Helicobacter pylori (H. pylori), the use of nonsteroidal anti-inflammatory drugs (NSAIDs), hyperacidity, use of alcohol and cigarette smoking (Bernersen et al. 1992, Karvonen & Lehtola 1983, Karvonen et al. 1987, Lehtola et al. 1988, O'Laughlin et al. 1981).

There are only a few reports describing the histopathology of gastric erosions. Nesland et al. (1986) studied erosive prepyloric changes, and found that a feature of acute inflammation always followed those erosions, which were diagnosed also by histological techniques, and fibrosis was found in all cases.

Erosions can be found in gastric mucosa that is either histologically inflamed or non-inflamed and this suggests that there is the existence of different phenotypes of gastric erosion disease (Karvonen & Lehtola 1983). The peptic ulcer risk associates with antrum predominant H. pylori gastritis, while risk of gastric cancer is linked with multifocal or body predominant atrophic gastritis. Finally body predominant gastritis exhibits a low peptic ulcer risk (Sipponen 2001, Uemura et al. 2001). The progression patterns of gastritis are related to both phenotype and associated complications, such as peptic ulcer as has been reported in follow-up studies (Maaroos et al. 1985, Niemelä et al. 1995a, Niemelä et al. 1995b, Valle et al. 1996). Currently, studies of evolution of gastritis in patients with gastric erosions are lacking, confirming the need for the current study.

The clinical importance of gastric erosions is that they may bleed; this symptom occurs up to 23% of cases (Laine 1998). Otherwise, gastric erosions are considered as harmless. However, erosions in gastric mucosa could be associated with clinically important local, distant, or systemic complications, and this was another reason for undertaking the current study.
2 Review of the literature

2.1 Orientating figures to the topic

Orientation of a scientific article can be difficult individuals not having special knowledge of the topic. To overcome this problem, here three figures will be shown to provide an basis for the remainder of this thesis (Figures 1–3).

Fig. 1. Schematic figure of different gastric anatomical regions.
Fig. 2. Examples of erosion findings as photographs. Type I (A), type IIa (B), type IIb (C) and type III (D) erosions are shown.
2.2 Definition of gastric erosion

Already in 1761, Morgagni utilized the term “erosion” in describing gastritis (Morgagni 1761). In 1950, a gastric erosion was defined as a superficial defect in the mucosa that did not penetrate through the muscularis mucosae layer (Ivy et al. 1950). In 1986, a workshop on the “Aggression to the Gastric Mucosa” was held at the World Congresses in Sao Paulo, Brazil, and there erosion was defined as a visible break in the mucosa (Laine & Weinstein 1988). The usual finding is a white base of erosion, although occasionally a blackened base may be seen as a mark of recent haemorrhage; the lesions are flat or minimally depressed and usually are surrounded by a narrow rim of erythema (Laine & Weinstein 1988). Erosion has also been described as a defect in the mucosa with a necrotic base that is less than 3–5 mm in diameter (Yardley & Hendrix 1995).

Microerosions are defects in epithelium, which can be revealed only by the microscope. They have been graded as follows: Grade 1, single cell dropouts are present; Grade 2, dropouts consisting of multiple cells are present. In addition, this grading extends to grade 3, in which there are real, endoscopically visible erosions, which are too large to be classified as microerosions (Leung et al. 1992).
The distinction of an erosion from an ulcer is based on the depth of the mucosal break. By definition, the ulcer penetrates the muscularis mucosae whereas an erosion does not. Endoscopically this is assessed in that the erosion does not interrupt the passage of the peristaltic wave in contrast with an ulcer. Another distinction can be seen when the margin of the erosion is grabbed with biopsy forceps, it can be lifted outwards because the floor of the erosion is not fixed to the gastric wall, as is in the case of an ulcer. During endoscopy, the estimation of depth of the mucosal break can only be an estimate. (Laine & Weinstein 1988, Roesch 1978).

Erosion should also be distinguished from other macroscopic changes visible in endoscopy. Erythema is defined as an area of redness. The mucosa is considered to be friable, if the endoscope induces subepithelial haemorrhages or oozing of blood. Subepithelial haemorrhage can be defined as petechiae or bright red areas, even though there is no visible break in the mucosa. (Laine & Weinstein 1988).

2.3 Classification

Gastric erosions has been classified according to chronicity, their endoscopical characteristics and scored by their severity. However, there is no agreement of the definition of acute and chronic gastric erosion. In this review, the term “chronic/recurrent erosion” refers to erosions found in both visits, which were nearly two decades separated from each other.

2.3.1 Endoscopic classification of gastric erosions

The classification is summarized in Table 1. Gastric erosions are divided into three categories: complete erosion, incomplete erosion and hemorrhagic-erosive gastritis (Roesch & Ottenjann 1970). The last of these three consists of numerous, pinpoint-sized haemorrhages on the mucosa and in addition within the mucosa and submucosa, erythrodiapedesis and engorged blood vessels. These may be diffuse or localized to the fundal or antral region.

Incomplete erosion has also been termed as a flat erosion and it is defined as a defect of the mucosa without any reaction of the surrounding mucosa (Kawai et al. 1970). A hematin-covered floor surrounded by an elevated border characterizes a complete erosion in the acute phase and it is usually followed within 48 hours by a whitish, gray-yellow coat (Roesch & Ottenjann 1970).
Incomplete erosions can further be divided into two subgroups: those located on the prominent folds of the prepyloric region (type IIb) and those located on flat mucosa (type IIa) (Karvonen et al. 1983). Nesland & Berstad (1985) defined erosive prepyloric changes (EPC) and divided these into three grades. EPC grade 1 was defined as a standing mucosal prepyloric fold, which is independent of peristalsis and runs transverse or parallel in relation to the antral lumen. EPC grade 2 was defined as red spots and/or streaks, which are situated on the top of the folds, in addition to the presence of grade 1 changes. EPC grade 3 was defined as former, and in addition, presence of macroscopic erosion. EPC grade 3 seems to correspond to type IIb erosions, which have been defined by Karvonen et al. (1983).

Kawai et al. (1970) subdivided complete erosions into two categories: a) mature type, in which the surrounding circular prominence is irreversible due to fibrosis and b) immature type, where it is due to oedema. Histology reveals that the latter may appear as foveolar pseudo-hyperplasia due to elongation of the crista. When re-epithelisation does take place, these changes disappear within a few days. (Roesch & Ottenjann 1970).

Varioliform gastritis is a rare condition in which there are multiple erosions (Laine & Weinstein 1988). They are typified by < 10 mm mucosal elevation with a central pale depression, and lesions are usually multiple at the crests of the folds of the antrum, body or both (Elta et al. 1983, Franzin et al. 1984, Freise et al. 1979, Green et al. 1982, Lambert et al. 1978). Lymphocyte gastritis can be manifested as this type of gastritis, mostly in the presence of normal antral mucosa (Stolte & Meining 2001).

Portal hypertensive gastropathy can resemble a gastric erosion finding, but in this case the histological findings are dilated superficial vessels without erosions or inflammation (Pique 1997). Similar haemorrhagic gastropathy have been detected during endoscopical examination in epidemic nephropathy (Nuutinen et al. 1992).
Table 1. Endoscopical classification of gastric erosions and gastric conditions with erosions as a predominant change.

<table>
<thead>
<tr>
<th>Main class</th>
<th>Subclass</th>
<th>Characteristic features</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Complete</td>
<td></td>
<td>Innumerable, pinpoint-sized hemorrhages on the mucosal surface</td>
<td>Roesch &amp; Ottenjann (1970)</td>
</tr>
<tr>
<td></td>
<td>Ia Mature type</td>
<td>The surrounding mucosal elevation is irreversible due to fibrosis</td>
<td>Kawai et al. (1970)</td>
</tr>
<tr>
<td></td>
<td>Ib Immature type</td>
<td>The bulging border is due to oedema</td>
<td>Kawai et al. (1970)</td>
</tr>
<tr>
<td>II Incomplete</td>
<td></td>
<td>A simple defect of the mucosal layer without reaction to surroundings</td>
<td>Roesch &amp; Ottenjann (1970)</td>
</tr>
<tr>
<td></td>
<td>Ila</td>
<td>Erosion located on flat mucosa</td>
<td>Karvonen et al. (1983)</td>
</tr>
<tr>
<td></td>
<td>Iib</td>
<td>Erosion located on the prominent folds of the prepyloric region</td>
<td>Karvonen et al. (1983)</td>
</tr>
<tr>
<td>III Haemorrhagic-erosive gastritis</td>
<td></td>
<td>Innumerable, pinpoint-sized hemorrhages on the mucosal surface with erythrodiapedesis and engorged blood vessels within mucosa and submucosa</td>
<td>Roesch &amp; Ottenjann (1970)</td>
</tr>
<tr>
<td>Erosive prepyloric changes (EPC)</td>
<td>EPC grade 1</td>
<td>Standing mucosal prepyloric fold, independent of peristalsis and running transverse or parallel into relation of antral lumen</td>
<td>Nesland &amp; Berstad (1985)</td>
</tr>
<tr>
<td></td>
<td>EPC grade 2</td>
<td>EPC grade 1 plus red spots and/or streaks situated on the top of the folds</td>
<td>Nesland &amp; Berstad (1985)</td>
</tr>
<tr>
<td></td>
<td>EPC grade 3 (equals Incomplete type)</td>
<td>EPC grade 2 plus the presence of macroscopic erosions</td>
<td>Nesland &amp; Berstad (1985)</td>
</tr>
<tr>
<td></td>
<td>Iib erosions</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2.3.2 Acute and chronic erosions

Gastric erosions can be found recurrently in the same subject, but it is not known, if these erosions are the same as seen before, or new ones. Thus these erosions can either be chronic or recurrent. There is no commonly accepted definition of what constitutes acute and chronic erosions.
2.4 Incidence and prevalence of gastric erosions

The exact incidence of gastric erosion is not known, but for example after ingesting 2.6 g of aspirin, all subjects were found to have submucosal haemorrhages or focal erosions within 24 hours (Graham et al. 1983).

2.4.1 Prevalence of erosions in asymptomatic subjects

In asymptomatic volunteers, the prevalence of gastric erosion has ranged from 3% to 12% (mean 7%; Table 2).

Table 2. Reports of the prevalence of gastric erosions in asymptomatic subjects. The mean prevalence and cumulative N are shown in the last row.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Erosion N</th>
<th>Total N</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>9</td>
<td>358</td>
<td>Ihmäki et al. (1979)</td>
</tr>
<tr>
<td>12</td>
<td>43</td>
<td>355</td>
<td>Akdamar et al. (1986)</td>
</tr>
<tr>
<td>9</td>
<td>10</td>
<td>113</td>
<td>Dooley et al. (1989)</td>
</tr>
<tr>
<td>4</td>
<td>13</td>
<td>310</td>
<td>Bernersen et al. (1992)</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>175</td>
<td>Lehmann et al. (2000)</td>
</tr>
<tr>
<td>7</td>
<td>89</td>
<td>1311</td>
<td></td>
</tr>
</tbody>
</table>

2.4.2 Prevalence in clinical series

In clinical series, the prevalence of gastric erosion has ranged from 4% to 49% (mean 15%; Table 3).

Table 3. Reports of the prevalence of gastric erosions in clinical series. The mean prevalence and cumulative N are shown in the last row.

<table>
<thead>
<tr>
<th>Prevalence</th>
<th>Erosion N</th>
<th>Total N</th>
<th>Publication</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>79</td>
<td>1859</td>
<td>Roesch &amp; Ottenjann (1970)</td>
</tr>
<tr>
<td>11</td>
<td>404</td>
<td>3837</td>
<td>Karvonen et al. (1983)</td>
</tr>
<tr>
<td>14</td>
<td>90</td>
<td>651</td>
<td>Nesland &amp; Berstad (1985)</td>
</tr>
<tr>
<td>7</td>
<td>21</td>
<td>309</td>
<td>Bernersen et al. (1992)</td>
</tr>
<tr>
<td>9</td>
<td>35</td>
<td>400</td>
<td>Heikkinen et al. (1997)</td>
</tr>
<tr>
<td>30</td>
<td>19</td>
<td>64</td>
<td>Auroux et al. (2003)</td>
</tr>
<tr>
<td>27</td>
<td>88</td>
<td>331</td>
<td>Duck et al. (2004)</td>
</tr>
<tr>
<td>23</td>
<td>198</td>
<td>869</td>
<td>Cheung et al. (2010)</td>
</tr>
<tr>
<td>49</td>
<td>502</td>
<td>1022</td>
<td>Ma et al. (2010)</td>
</tr>
<tr>
<td>15</td>
<td>1436</td>
<td>9342</td>
<td></td>
</tr>
</tbody>
</table>
In autopsy series, the prevalence of hemorrhagic gastric erosion has been reported to be 5% (546/11352) (Martinoli & Gantner 1970).

### 2.5 Aetiology of gastric erosions

An erosion is formed either as a consequence of epithelial cell death or of epithelial detachment, resulting in loss of epithelial cells that exceeds the epithelial regeneration capacity. Secondly, the loss of epithelial cells evokes luminal factors e.g. gastric acid release which can start to destroy subepithelial structures. This kind of loss of mucosal integrity can be induced by several chemicals, diseases and mechanical or physical factors. Table 4 lists presumed etiological factors.

<table>
<thead>
<tr>
<th>Chemicals</th>
<th>Diseases</th>
<th>Mechanical/Physical factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Crohn’s disease</td>
<td>Endoscopic haemostasis</td>
</tr>
<tr>
<td>Gastric acid</td>
<td>Diabetes mellitus type II</td>
<td>Gastric band</td>
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<td>Iron preparations</td>
<td>Duodenogastric reflux of bile acid</td>
<td>Nasogastric tube</td>
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<td>NSAID</td>
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<td>Osteoporosis treatment</td>
<td>Herpes simplex infection</td>
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<td>Potassium chloride</td>
<td>Mini early carcinoma and lymphoma</td>
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<td>Smoking</td>
<td>Rare infections (Syphilis, CMV, Tuberculous)</td>
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#### 2.5.1 Herpes simplex virus

**Animal studies**

Oral inoculation with HSV-1 evoked gastric ulcers in mice, and one of the 40 ulcers contained viral Ag. However, the remaining ulcers were situated adjacent to virus-infected ganglia (Gesser et al. 1995). After placement of HSV-1 into the oesophageal lumen of mice, the HSV-1 virus could spread via internodal strands of the enteric nervous system, leading to infection of the neurons of plexuses of the stomach. HSV-1 labelled terminal nerve fibres penetrate into the lamina propria of the gastric mucosa allowing a direct interaction with surface epithelial cells (Gesser & Koo 1996).
**Human studies**

Latent HSV-1 have been found in humans in the ganglia innervating the gastrointestinal (GI) tract and these viruses have also been found in gastric ulcers or in their immediate proximity in 9%-32% of cases. However, it is not certain whether this is an etiologic factor, a cofactor or an opportunistic factor (Kemker et al. 1992, Tsamakidis et al. 2005, Warren et al. 1978). Herpes related lesions recur when the latent virus in the ganglia travels along the nerve causing a recurrent lesion (Docherty & Chopan 1974). It has been claimed that it is possible to interrupt this migratory pathway by severing the nerve (Kemker et al. 1992). However, there are no reported trials on the effects of anti-HSV treatment in therapy of gastric erosions or ulcers.

### 2.5.2 Helicobacter pylori

The role of *H. pylori* infection as an etiological factor for gastric erosion is controversial and the conclusions seem to depend on that how erosions and ulcers have been differentiated.

Ulcers and erosions have been reported to disappear after eradication of *H. pylori* (Chan et al. 2001). In a histological analysis, *H. pylori* gastritis was present in 99% of patients with complete erosions of the antral mucosa (Stolte & Eidt 1992). Erosive prepyloric changes grade 3 findings were observed more frequently in *H. pylori*-infected than in non-infected subjects, although the difference was not statistically significant (Berstad et al. 1988). It has been reported that there is an increased *H. pylori* density in erosions, and also it has been claimed that there are differences in the genotype distribution compared to unaffected regions (Molnar et al. 2008).

There are some observations opposing a role for *H. pylori* as a causative agent in gastric erosions. Gastroduodenal erosions in asymptomatic volunteers have been found with equal frequencies in *H. pylori*-positive and -negative subjects, and in another study with asymptomatic volunteers, only 4 of 14 subjects with gastric erosions were found to be infected with *H. pylori* (Dooley et al. 1989, Lehmann et al. 2000). In contrast, nearly half of 34 EPC grade 3 subjects were infected with *H. pylori* (Bernersen et al. 1992). Two more recent studies also failed to detect any clear relationship between macroscopic erosions and *H. pylori* infection (Ma et al. 2010, Szoke et al. 2008). It has even been
suggested that a *H. pylori* infection may protect from gastric erosions in patients with end-stage renal failure (Moriyama *et al.* 2010).

### 2.5.3 Non-steroidal anti-inflammatory drug

Volunteers treated with acetasalicylic acid (ASA) can develop erosive lesions within 24 hour (Graham *et al.* 1983, O'Laughlin *et al.* 1981). Incomplete type IIa erosions have been associated with the use of analgesics (Karvonen & Lehtola 1983). It has been reported that there are similar numbers of gastric erosions after the use of Cox-2 selective drugs and non-selective NSAID preparations (Cheung *et al.* 2010). After 12 weeks’ use of celecoxib and diclofenac, at the endpoint almost the same number of subjects had developed gastric erosions; 21% (85 of 434) in the celecoxib group and 23% (91 of 435) of those receiving diclofenac. In fact, there are even reports that fail to show relation between gastric erosions and the use of NSAIDs (Dooley *et al.* 1989, Gallagher *et al.* 1987, Lehmann *et al.* 2000, Pazzi *et al.* 1994).

The mechanism of NSAID/ASA-induced erosions is proposed to be mainly inhibition of prostaglandin synthesis and oxidative phosphorylation, but also disturbances in the local microcirculation, resulting in ischemic necrosis, have been proposed (Bjarnason *et al.* 1993, Kitahora & Guth 1987, Sanchez *et al.* 2002, Vane 1971). It is postulated that an acid independent component in NSAID gastropathy causes microscopic erosions that are related to the inhibition of prostaglandin synthesis (Whittle 1981).

Long-term NSAID users infected with *H. pylori* develop significantly more erosions as compared to patients not infected with *H. pylori*, but this is a matter of controversy (Graham *et al.* 1991, Taha *et al.* 1995). Low-dose ASA users not infected with *H. pylori* had more frequently gastric erosions compared to *H. pylori* infected; hence a *H. pylori* infection may possess some protective effect against low-dose ASA-induced gastric erosions (Hart *et al.* 2010). The speculative mechanism for this phenomenon can be damage to the parietal cells having a putative lower production of acid. The risk of erosions did not increase with aging (Hart *et al.* 2010).

### 2.5.4 Gastric acid

Roesch & Ottenjann (1970) reported that most patients with gastric erosions displayed hyperacidity and this correlated well with their observation that
atrophic gastritis was uncommon in patients with erosions. However, another study in EPC patients reported that the mean acid output values did not differ from values of healthy subjects (Nesland & Berstad 1985). In addition, another study showed that in patients with prepyloric erosions the body mucosa was well preserved despite aging and this observation is similar to the situation in patients with duodenal ulcers. The authors proposed that there would be a common acid-related pathogenesis (Karvonen et al. 1987).

Studies which have taken into account *H. pylori* infection, have demonstrated that too much gastric acid can lead to peptic ulcers and stress-related erosions/ulcers (Schubert 2010).

Recovery of acid secretion capacity after *H. pylori* eradication has been believed to be involved in the development of gastric erosions. Miyake et al. (2005) observed that the development of gastric erosions after eradication depended on whether there was less severe corpus atrophy or more severe corpus gastritis. On the other hand, treatment with H2 blocker has been claimed to decrease the rate of erosions (Miyake et al. 2002).

### 2.5.5 Other factors

Although there are believed to be several genetical risk factors for peptic ulcer such as polymorphisms in immunoregulatoratory genes, only a few studies have addressed genetic factors in gastric erosion (Shiotani et al. 2010). The G-308A polymorphism of TNF-alpha, which causes elevated expression of the TNF-α protein (G/G genotype), has been associated with erosive gastritis (Szoke et al. 2008). In contrast, CD14 genetic polymorphism showed no association with the risk of gastric erosions (Karahukorpi et al. 2002).

**Chemicals**

*Alcohol.* Gastric erosions are a common finding in patients with chronic alcoholism (Segawa et al. 1987, Uppal et al. 1991). Erosive prepyloric changes have been reported to be common in women using alcohol (Bernersen et al. 1992).

*Iron* containing preparations. In a study with 14 healthy volunteers that ingested ferrous sulphate for two weeks, two subjects developed solitary antral erosion (Laine et al. 1988).
Osteoporosis treatment. Alendronate 10 mg daily was reported to cause gastric erosions in a minority of subjects during 2 weeks (Graham & Malaty 1999).

Potassium chloride. It has been reported that potassium chloride can induce gastric erosions (McMahon et al. 1982).

Smoking. Smoking has been claimed to be common in erosion patients (Karvonen & Lehtola 1983). Erosive prepyloric changes have been reported to associate with cigarette smoking (Bernersen et al. 1992).

Diseases

Crohn’s disease. In patients with Crohn’s disease, endoscopically observed erosions have been reported to be a usual finding, and these can be of predictive value for the presence of granulomas (Schmitz-Moormann et al. 1985). The histologic features, which are suggestive of Crohn’s disease, include focal active gastritis and granulomatous gastritis (Parente et al. 2000, Yardley & Hendrix 1995).

One study of patients with diabetes mellitus type II, which is characterized by high risk of vascular disease, found that their 21 out of 72 patients suffered gastric erosions (Boehme et al. 2007).

Duodenogastric reflux of bile acids. Intragastric administration of bile into the rat was shown to produce gastric erosions (Mann 1976).


Rare infections. Syphilitic gastritis has been reported in over 100 patients in the literature. A typical syphilitic gastritis patient is a young adult with gastric pain, in whom syphilis should be suspected if endoscopy reveals gastric erosion or shallow gastric ulcer with extensive gastritis in histology (Kim et al. 2009). A case of cytomegalovirus infection appearing as acute gastroduodenitis including gastric erosions has been reported with the diagnosis being confirmed with positive anti-cytomegalovirus antibody staining (Shirakami et al. 2007). A case of tuberculosis with gastric erosion accompanied by bleeding has also been reported (Rathnaraj et al. 1997).
Mechanical and physical factors

Gastric Band. Although a gastric band has been reported to erode only in a minority, it may require the removal of the gastric band (Yoon et al. 2012).

Nasogastric tube and endoscopic haemostasis. Nasogastric tubes commonly cause gastric erosions, and different endoscopic haemostasis techniques have also been reported to cause gastric erosion in the areas being treated (Weinstein 1998).

2.5.6 Factors affecting chronicity

Many of the studies that have discussed factors affecting the chronicity of gastric erosion predate the awareness of *H. pylori*, which is an important factor in chronic gastritis. An elevated gastric acid secretion capacity has shown to be associated with erosion chronicity, although this was statistically significant only in the incomplete type of erosions (Karvonen & Lehtola 1984).

2.6 Pathogenesis of gastric erosions

As the aetiology of gastric erosion is multifactorial, so too the pathogenesis also seems to be multifactorial. Erosions are a result of an imbalance between protective and destructive factors. Erosion and ulcers can be considered to be the same process and it is likely that they share common factors evoking mucosal damage. The factors that participate in the pathogenesis of gastric ulcer can be divided into luminal, epithelial cell, apoptotic and regenerative factors.

Luminal factors. Gastric acid is most important luminal factor. It is well known that there is hyperacidity in stress ulcers (Fenoglio-Preiser et al. 2008). Secondly, there is elevated pepsin formation (Feldman et al. 1988). Thirdly, increased retrograde peristaltic waves with low pyloric tone and reduced local motility can lead to more intensified biliary and pancreatic duodenogastric reflux (Flint & Grech 1970). The levels of endothelins are increased in saliva in peptic ulcer patients and this may contribute to the pathogenic process (Lam et al. 2004). Saliva itself can be considered to participate in offering protection against peptic ulcers (Malhotra 1970). In erosions patients, the mucoprotective index (the ratio of neutral to total mucoproteins) has been reported to be decreased, and weakening of mucosal defences has been speculated to be a major factor in the pathogenesis of gastric erosions (Guslandi et al. 1989).
Epithelial cells and mucus. Protection against gastric acid is provided by epithelial cells which secrete mucus and bicarbonate (Soll 1990). When gastric protective mechanisms are activated then epithelial production of mucus and bicarbonate increases (Holle 2010). Mucosal cells possess a membrane that resists acid from returning into the cell (Soll 1990). Mucosal protection becomes weakened when there is a decline in mucus secretion, mucosal blood flow, the synthesis of DNA and prostaglandins. This changes the mucus composition and low molecular glycoprotein production increases, leading to conditions favouring proteolysis and rediffusion of H⁺-ion, which then enhance ulcer formation (Holle 2010, Younan et al. 1982). Damage to the mucosal barrier results in tissue acidosis, congestion of mucosa and necrosis (Fenoglio-Preiser et al. 2008).

Increased apoptosis leading to loss of mucosal integrity is one factor in the development of ulcers ((Leung et al. 2000). When reperfusion takes place, then neutrophils can produce toxic oxygen free radicals (Fenoglio-Preiser et al. 2008). Ischemic stress related erosions are encountered mainly in intensive care patients. It has been reported that brain ischemia in rats can produce gastric hemorrhagic erosions through gastric oxidative stress and activation of the arginine-nitric oxide pathway (Hung 2006).

Epidermal growth factor has been reported to stimulate mucosal cell proliferation and also inhibit acid secretion (Holle 2010).

Regeneration. Ulcer associated cell lineage (UACL) has been found at sites of chronic gastric ulcers. Gastric stem cells induce UACL and this assists in the healing of the ulcer. This involves coordinated localisation of mucins and trefoil peptides, which are potent mitogens of GI epithelium in conjunction with epidermal growth factor (Longman et al. 2000, Patel et al. 1994). In addition, healing can be assisted also by an increased mucosal blood flow (Fenoglio-Preiser et al. 2008).

2.7 Histopathology of gastric erosions

Erosions are histopathologically characterized by epithelial defects extending into the deeper layers of the mucosa. An erosion is formed either as a consequence of epithelial cell death (necrosis or apoptosis) or of epithelial detachment, i.e. the level of apoptosis or detachment is in excess of the magnitude of epithelial regeneration. Detached epithelium alone defined as erosion can be misleading because of biopsy induced artefacts, and the definition of erosion should always include other features of erosion, for example fibrinoid necrosis or granulated
tissue (Laine & Weinstein 1988). There is no acknowledged histopathological classification for gastric erosions, except for the classification of microerosions. Furthermore, previously little was known about the prognostic value of histological findings of the erosion.

In addition to the abovementioned factors, there are many reports of scattered histological findings in erosion. Erosions have been noted to contain fibrin deposition, neutrophilic infiltration and there may be regenerative changes in the adjacent epithelium (Dixon et al. 1996). It has also been reported that NSAID/ASA erosions consist of a homogeneous eosinophilic ischemic necrosis blending into the adjacent lamina propria, whereas in H. pylori-induced erosions, the erosive defects are covered with inhomogeneous fibroid necrosis that does not blend into the adjacent lamina propria and they also contain cell debris and granulocytes (Stolte et al. 1999). Stress induced erosions are characterized histologically by epithelial necrosis, with a fibrin exudate and the presence of neutrophils (Czaja et al. 1975). Foveolar hyperplasia has also been described (Pazzi et al. 1994). EPC grades 2 and 3 have been reported to manifest with infiltration of neutrophils, fibrosis, lymphocytes and plasma cells (Nesland et al. 1986). Kawai et al. (1970) reported that a subset of erosions displays signs of fibrosis.

2.8 Gastritis in patients with erosion

2.8.1 Definition of gastritis and classification

Gastritis is defined as a microscopic inflammation of the stomach, and it is a histological, but not a clinical, entity.

The most widely used classification of gastritis is the updated Sydney system, which classifies gastritis according to the topography, morphology and aetiology. Chronic gastritis is divided in nonatrophic, atrophic (autoimmune and multifocal) and special forms of gastritis (i.e. chemical, radiation, lymphocytic, non-infectious granulomatous, eosinophilic and other infectious gastritides); also other forms differing from chronic gastritis have been defined. (Dixon et al. 1996).
2.8.2 Phenotypes and dynamics of gastritis

Apart from normal gastric mucosa, even without *H. pylori* infection, topographic phenotypes of *H. pylori* gastritis and atrophic gastritis are classified as follows (Sipponen 2001, Stolte & Meining 2001):

*Ulcer phenotype* *H. pylori* gastritis consist of two forms. *Gastritis in patients with duodenal ulcer*, in which the corpus mucosa is nonatrophic and especially in the antrum there is evidence of gastritis (*antrum predominant gastritis*), and the surface epithelium displays lesions, which are degenerative and regenerative, especially in the antrum and in one fifth of cases there is also intestinal metaplasia and atrophy. In this pattern of gastritis, there is a high level of acid secretion. *Gastritis in patients with gastric ulcer gastritis* (*corpus predominant gastritis*) differs from the above-mentioned type and tends to be diffuse, possibly with multifocal atrophy and intestinal metaplasia (*multifocal atrophic gastritis*). The stomach may also show hypochlorhydria and it may resemble the gastric cancer phenotype gastritis. However, even the antral gastritis seems to advance in patients with gastric ulcer (Niemelä *et al.* 1995a).

*Gastric cancer phenotype of gastritis*, where advanced atrophic gastritis and intestinal metaplasia occur multifocally (*multifocal atrophic gastritis*), there can be low production of gastric acid and the risk of gastric neoplasia is increased. In some cases, despite positive serology, the histological search for *H. pylori* may be negative. Lymphocytic gastritis has also been shown to associate with gastric cancer and lymphoma, possibly due to its tendency to progress in severity and due the presence of metaplastic changes in the body mucosa (Miettinen *et al.* 1995).

The dynamics of gastritis seems to modify the risk of complications. Corpus predominant gastritis tends to lead to atrophy and cancer, and antrum predominant gastritis in turn, tends to predispose to peptic ulcer.

The reasons for the individual different outcomes of *H. pylori* infection are largely unclear. The different topographic distribution of gastritis in *H. pylori* infection has been explained by differences in bacterial factors, such as virulence factors (e.g. cagA status) and the extent of colonization, host factors e.g. genetic factors such as interleukin-1 gene cluster polymorphism, and the interaction between these two factors. In addition, host-microbial interaction and environmental factors have been postulated, and the final outcome may be multistaged (Blaser *et al.* 1995, El-Omar *et al.* 2000, Garcia-Gonzalez *et al.* 2001, Maaroos *et al.* 1994, Nomura *et al.* 2002, Peek & Blaser 2002).
2.8.3 Gastritis in erosion patients

Atrophic antral gastritis is reported to be rare in erosion patients (Karvonen et al. 1983). However gastritis in chronic erosion patients is strongly dependent on the presence of *H. pylori* infection, but few studies have taken into account the *H. pylori* status. Patients with EPC grade 3 are reported to experience more chronic atrophic gastritis and more subacute gastritis than those without EPC (Bernersen et al. 1992).

2.8.4 Dynamics of gastritis in erosion patients

The dynamics of gastritis in erosion patients is largely unknown. A slow progression of antral gastritis in gastric erosion patients has been reported, with increasing body gastritis with age. However, prepyloric erosions, similar to those encountered in duodenal ulcer patients, did not show this progression of body gastritis. Unfortunately this study was mainly done before the era of awareness of *H. pylori* (Karvonen et al. 1987).

2.9 Follow-up studies in gastric erosion

There are only a few follow-up studies examining gastric erosions. One study had follow-up of six years; two thirds of erosions healed and two patients developed new hyperplastic polyps, and there was no correlation between symptoms and erosion findings. In that study, type IIb erosions only healed in 38% of cases (Karvonen & Lehtola 1984). After a mean of 45 months of follow-up of grade 3 erosive prepyloric changes, most patients still had dyspeptic symptoms (92%; 21/23), and grade of EPC (61%; 14/23) remained unchanged, and patients were also without complications such as ulcers (Stene-Larsen et al. 1989).

2.10 Clinical significance of gastric erosions

The clinical significance of gastric erosion has been only examined to a limited extent and those studies have largely focused on gastritis and ulcers. To a lesser degree, erosions have been evaluated and the distinction between erosion and ulcer might well be blurred. These considerations further emphasize the need for studies focusing on the clinical importance and course of gastric erosions.
2.10.1 Symptoms

There are some publications, which suggest that gastric erosions associate with dyspeptic symptoms (Nesland & Berstad 1985, Stene-Larsen et al. 1989). On the other hand, it has been proposed that in the majority of cases, gastric erosions seem to evoke no symptoms (Larkai et al. 1987, Lehmann et al. 2000). The mechanisms behind what symptoms do appear are not clear. Since there are no sensory nerves in the gastric mucosa, simple mucosal destruction does not explain the symptoms. Since erosions obviously do not correlate with symptoms, ulcers also do not correlate well with symptoms (Aro et al. 2006). In population living in northern Sweden, peptic ulcers have been reported to be asymptomatic in 20% of cases (Aro et al. 2006).

2.10.2 Bleeding

In one study a total of 12,392 gastroscopies were performed for evaluation of nonvariceal hematemesis, melaena or suspected upper GI bleeding and the most common finding was ulcer (33%) followed by erosion in 19% of subjects (Enestvedt et al. 2008). Among 2097 patients endoscoped for upper GI bleeding, 30% (620 patients) displayed gastric erosions and of these, active bleeding was reported in 27% (166/613). (Gilbert et al. 1981).

2.10.3 Ulcer risk

In a study with a follow-up of up to 6 years monitoring gastric erosion patients, only 4% (4 of 105) had acquired gastric ulcer (Karvonen & Lehtola 1984). In another study with a mean of nearly 4 years of follow-up of 60 patients with EPC, none of the subjects developed peptic ulcer (Stene-Larsen et al. 1989). Finally, it has been reported that long-term NSAID users with gastric erosions develop more often peptic ulcer than those without erosions (Taha et al. 1995).

2.10.4 Malignancy

There are no follow-up studies with adequate follow-up times investigating malignancy risk in patients with gastric erosions.
3 Aims of the study

Gastric erosions are one of the most prevalent gastroscopic abnormalities, and among the most important causes of GI bleeding. Rather incomplete information about the long-term course of gastric erosions is available, and in addition, nothing is known about the pathogenetic factors leading to delay of healing or chronicity of erosions as well as the clinical significance of chronic erosions. The purpose of this study was to focus on these aspects of gastric erosions by using a long-term follow-up study setting. The detailed aims are as follows:

1. To determine the rate of chronic/recurrence of gastric erosions in a long-term follow-up setting.
2. To investigate the aetiology of chronic/recurrent gastric erosions, including HSV infection, *H. pylori* infection, and the use of NSAIDs.
3. To characterize the histopathology of gastric erosion and gastritis in patients with gastric erosion, and to determine features related with prognosis of erosions.
4. To define clinical significance of chronic/recurrent and non-recurrent gastric erosion.
4 Materials and Methods

Numerals (I-IV) are referring to scientific articles belonging to this thesis:

4.1 Patients

The patients and controls were recruited from those referred for elective gastroscopy in the Gastroenterologic Unit of the Department of Internal Medicine, University Central Hospital of Oulu, during a period of five years (Sept. 1 1974 - Aug. 31 1979). The series consisted of 3837 patients (2080 males). Gastric erosions were diagnosed in 404 subjects. Those subjects with erosions concurrent with peptic ulcer disease (N = 129), any GI disease requiring specific or urgent treatment (N = 16) or some serious disease (N = 21) were excluded. In addition, 121 patients were also excluded because of inadequate co-operation, poor tolerance of gastroscopy, difficulties in attending the follow-up examination, or refusal to attend further examinations. Altogether 287 patients were excluded from the original series. Thus a final total of 117 patients (63 males) with erosion as the predominant finding were included and invited to a re-examination in 1996.

4.2 Controls

For each patient, a control of the same age (± 5 years) and sex (except one woman instead of a man) was drawn prospectively from subjects gastroscoped electively in the same department during 1979 - 1981 and not diagnosed as having gastric erosions, peptic ulcer disease or any other severe disease of the GI tract or other organs requiring immediate treatment. The control group consisted of 117 patients (62 males).

4.3 Endoscopy and biopsies

Upper GI endoscopy was performed both at the initial visit (years 1974–1981) and at the follow-up visit (1996). In the initial and follow-up visit, two biopsies were taken from the greater curvature of the antrum and the corpus, avoiding areas of macroscopical erosions. In the follow-up visit, two additional biopsies were taken from the lesser curvature of the antrum and corpus. Furthermore, separate biopsies were taken from macroscopically visible erosions. All biopsies
were fixed in neutral buffered formalin and embedded in paraffin. The sections were stained with modified Giemsa and Hematoxylin-Eosin.

The erosions were diagnosed and classified according to established criteria by the dominant type as follows (Roesch & Ottenjann 1970). Type I (complete erosion): erosion elevated above the surrounding mucosa and surrounded by a marginal wall. Type II (incomplete erosion): erosion located on even mucosa and often surrounded by a reddish margin. Type III (haemorrhagic-erosive gastritis): several small haemorrhagic erosions on even mucosa. Erosions were classified as chronic/recurrent if they were endoscopically visible on both visits. Also all other endoscopic findings were recorded according to the protocol.

4.4 Histological assessment of gastritis

According to the histological criteria of the updated Sydney-system, activity and severity of gastritis were scored by using a scale from normal or absent (score 0), to slight (score 1), moderate (score 2) and severe (score 3) change or increase (Dixon et al. 1996). Atrophy was scored as absent (score 0), slight (score 1), moderate (score 2) and severe (score 3). The presence of eosinophils, vasodilatation, lymphoid follicles, germinal centres, fibrosis and foveolar hyperplasia was scored as absent (score 0), slight (score 1), moderate (score 2) and severe (score 3). Lymphocytic gastritis was diagnosed (score 2), if the count of intraepithelial lymphocytes was at least 25/100 epithelial cells. The extent of intestinal metaplasia was expressed as the percentage of mucosa showing intestinal metaplastic epithelium. The presence and severity of intraepithelial neoplasia (dysplasia) were assessed as absent (score 0), mild (score 1), moderate (score 2) and severe (score 3), and they were recoded as low-grade (scores 1 and 2) or high-grade (score 3) (Fenoglio-Preiser et al. 2000). Metaplastic and nonmetaplastic intraepithelial neoplasias (dysplasia) were evaluated separately. Microscopic erosions were scored by using a scale as absent (score 0), mild (single cell dropouts present; score 1), moderate (dropouts of several cells; score 2) or true erosions (score 3) (Leung et al. 1992). The percentage of surface epithelial cells showing tufting was estimated (Chan et al. 1991). The reactive gastritis score was calculated (Dixon et al. 1986). In addition, biopsies from erosions were assessed separately from the other biopsies with the assessor being blinded to the observations made from the non-eroded mucosa. One investigator (TJK) performed all histological analyses and he was blinded to the clinical data.
Specimens of the initial and follow-up endoscopy were evaluated separately, with the investigator being blinded to the results of the corresponding analyses.

4.5 Evaluation of *Helicobacter pylori* infection and Herpes simplex virus infection

*H. pylori* infection was diagnosed at both visits from the biopsy specimens taken from the antral and body mucosa using Giemsa and Hematoxylin-eosin staining.

Antibodies to HSV at both visits were measured of sera by using the complement fixation method with a commercial antigen (Bio Whittaker, Walkersville, USA). Titres of one to $\geq 32$ in the initial and $\geq 16$ in the follow-up visit were designated as “high titre”, based on values of all the samples and their normal distribution.

Formalin fixed, paraffin embedded biopsy specimens representing erosions taken at the follow-up visit were used for HSV immunohistochemistry and polymerase chain reaction (PCR). The sections were deparaffinised and stained with specific rabbit antibodies against HSV-1 and HSV-2 (BioGenex, San Ramon, Ca, USA) using avidin-biotin detection system and diaminobenzidine as a chromogen (Dako ABC kit, Dako, Copenhagen, Denmark). No antigen retrieval system was used. The dilution of primary antibody was 1:400 with an incubation time at room temperature of one hour. A specimen from herpetic esophagitis was used as a positive control. Phosphate buffered saline was used instead of primary antiserum as a negative control.

For HSV PCR, the parafin in the biopsy specimens was removed with xylene, and DNA was isolated using proteinase K digestion following phenol extraction and ethanol precipitation. The primer pair used in PCR was chosen from the polymerase gene for HSV-1 and HSV-2 (Piiparinen & Vaheri 1991). In each run, positive and negative controls were included. The amplified products were detected by microplate hybridization using specific probes for HSV-1 and HSV-2 (Vesanen et al. 1996).

4.6 Symptoms and other clinical data

On both visits, the investigators interviewed the subjects and pertinent anamnestic and clinical data from the local hospital were recorded using a questionnaire. A routine clinical abdominal status was also conducted.
On both visits, the type and duration of abdominal pain were evaluated and inquired as described earlier (Karvonen & Lehtola 1983). During the follow-up visit, the type of dyspepsia (reflux/ ulcer/ motility/ non-specific) was specified (Drossman et al. 1990). A patient history of diseases was recorded on each visit. In particular, clinically identified GI diseases, including GI bleeding during the follow-up period, and gastric or other abdominal surgery were recorded.

The use of all medication for abdominal diseases or symptoms was asked at both visits. The most recent use of NSAID was registered (< 24 hours, 1–3, 4–7 or > 7 days before endoscopy). Any use of an NSAID within the past 7 days was designated as recent use. Drugs for other diseases and the possible use of \textit{H. pylori} eradication treatments were inquired. Smoking habits and the use of alcohol were recorded. Family history in first-degree relatives of gastric cancer, gastric or duodenal ulcers and other GI diseases was registered.

4.7 Blood chemistry

Erythrocyte sedimentation rate, leukocyte count, serum C-reactive protein, haemoglobin, creatinine, alanine aminotransferase, and alkaline phosphatase were measured at both visits by routine methods. (I-IV)

In the initial visit, serum parietal cell antibodies were examined using the polyvalent antihuman immunoglobulin fluorescein conjugate (Roboz®). (III)

4.8 Occurrence of Malignancies, Mortality and Causes of Death

The Finnish Cancer Registry (Helsinki, Finland) was contacted to obtain data on the occurrence of malignant diseases (II, IV). Statistics Finland (Helsinki, Finland) provided data of mortality and causes of death (IV).

4.9 Statistical analysis

The statistical analysis was carried out using a statistical program (SPSS for Windows Release 8.0–14.0, and SPSS 16.0 for Macintosh, SPSS Inc., Chicago, Illinois, USA). The analysis of categorized variables was carried out by the $\chi^2$ and Fischer’s two-sided exact tests. Differences were considered as significant at $p$ values < 0.05 in two-tailed tests. Mann-Whitney U-test was used for the analysis between groups of the scored variables and Wilcoxon paired rank sum test was used for the analysis of temporal changes in the scored variables. The
nonparametric Spearman rho test was used for estimation of correlations. The estimations of the relative risk of erosion association with HSV infection, the recent use of NSAIDs and existence of *H. pylori* infection were carried out with logistic regression analysis. Kaplan-Meier Log Rank test was utilized to calculate mortality and malignancy data.

### 4.10 Ethical consideration

The study was approved by the Ethical Committee of the Medical Faculty of the University of Oulu. All subjects who participated in the study signed an informed consent.
5 Results

5.1 Final study groups

The characteristics of the final study groups are summarized in Figures 4 and 5.

All of the 117 patients and 117 controls of the original series studied in 1974–1981 were included after 16 years of follow-up in the analysis of mortality and the occurrence of malignant tumours.

The follow-up visit was arranged in 1996 and 54 (46% of the original series) of the 117 patients agreed to take part in an interview, a clinical assessment and routine blood tests. Of the controls, 70 (60% of the original series) were available for follow-up analyses in 1996 (IV).

From \textit{H. pylori}-positive subjects in the initial visit, 16% (5 of 32) of patients and 31% (14 of 45; 33% 15 of 46 in III) of controls had changed to being negative in the follow-up endoscopy. From \textit{H. pylori}-negative subjects in the initial visit, 12% (2 of 17) of patients and 11% (2 of 18; 12% 2 of 17 in III) of controls had changed to being positive in the follow-up endoscopy. Subjects with a changed \textit{H. pylori} status were excluded from the analysis of the effect of \textit{H. pylori} infection. (I-III).

After the exclusions, the final study group consisted of 42 patients and 47 controls (I, 46 controls in III, IV). The mean follow-up was 19 years (range 16.7–21.4 years) in the patient group and 16 years (range 15.1–19.0 years) in the control group (I,III).

It was possible to evaluate the histopathology from erosions and background antral mucosa in 52 \textit{H. pylori}-positive and in 31 \textit{H. pylori}-negative patients at the initial visit, but at the follow-up visit, there were only 7 \textit{H. pylori}-positive and 3 \textit{H. pylori}-negative patients with erosion, making it impossible to make comparisons within \textit{H. pylori}-positive or negative groups. Comparison analysis of chronic/recurrent and non-chronic/non-recurrent erosions was possible in 28 patients; of those, 10 were patients with chronic/recurrent erosions and 18 were patients with non-chronic/non-recurrent erosions. (II; Figure 5).
Fig. 4. Summary of patients and controls in the initial visit 1974–79 and in the follow-up visit 1996 (I, III-IV). Revised *H. pylori* status listed in square brackets concerning publications III-IV.
Fig. 5. Summary of patients examined in the initial visit in 1974–79 and in the follow-up visit in 1996 (II).

<table>
<thead>
<tr>
<th>Patients at the initial visit N = 117</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 63 men, mean age 48 (SD ± 10.8) years</td>
</tr>
<tr>
<td>- 54 women, mean age 50 (SD ± 10.5) years</td>
</tr>
<tr>
<td>- 70 H. pylori-positive</td>
</tr>
<tr>
<td>- 46 H. pylori-negative</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excluded N = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td>one missing H. pylori status</td>
</tr>
<tr>
<td>18 H. pylori-positive patients</td>
</tr>
<tr>
<td>- 6 erosions not located in the antrum</td>
</tr>
<tr>
<td>- 12 no erosion histology samples available</td>
</tr>
<tr>
<td>15 H. pylori-negative patients</td>
</tr>
<tr>
<td>- 4 erosions not located in the antrum</td>
</tr>
<tr>
<td>- 11 no erosion histology samples available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Initial visit cross-sectional comparison N = 83</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 52 H. pylori-positive (63%)</td>
</tr>
<tr>
<td>34 males, mean age 49 (SD ± 10.5) years</td>
</tr>
<tr>
<td>18 females, mean age 50 (SD ± 8.4) years</td>
</tr>
<tr>
<td>- 31 H. pylori-negative</td>
</tr>
<tr>
<td>15 males, mean age 46 (SD ± 10.8) years</td>
</tr>
<tr>
<td>16 females, mean age 49 (SD ± 11.2) years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Excluded N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>22 died</td>
</tr>
<tr>
<td>20 did not want to participate</td>
</tr>
<tr>
<td>2 refused to undergo endoscopy</td>
</tr>
<tr>
<td>2 had anticoagulation treatment (Marevan®)</td>
</tr>
<tr>
<td>4 had changed to H. pylori-positive</td>
</tr>
<tr>
<td>2 had changed to H. pylori-negative</td>
</tr>
<tr>
<td>3 if erosion present, no biopsy obtained</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up visit N = 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 20 H. pylori-positive (71%)</td>
</tr>
<tr>
<td>13 males, mean age 62 (SD ± 7.5) years</td>
</tr>
<tr>
<td>7 females, mean age 68 (SD ± 6.0) years</td>
</tr>
<tr>
<td>- 8 H. pylori-negative</td>
</tr>
<tr>
<td>4 males, mean age 62 (SD ± 8.0) years</td>
</tr>
<tr>
<td>4 females, mean age 64 (SD ± 6.5) years</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No erosion at follow-up visit N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;non-chronic/non-recurrent erosion&quot;</td>
</tr>
<tr>
<td>- 13 H. pylori-positive</td>
</tr>
<tr>
<td>mean age 63 years (SD ± 6.0)</td>
</tr>
<tr>
<td>5 females, 8 males</td>
</tr>
<tr>
<td>- 5 H. pylori-negative</td>
</tr>
<tr>
<td>mean age 62 years (SD ± 6.7)</td>
</tr>
<tr>
<td>2 females, 3 males</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Erosion at follow-up visit N = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;chronic/recurrent erosion&quot; and patients for follow-up cross-sectional comparison</td>
</tr>
<tr>
<td>- 7 H. pylori-positive</td>
</tr>
<tr>
<td>mean age 65 years (SD ± 10.3)</td>
</tr>
<tr>
<td>2 females, 5 males</td>
</tr>
<tr>
<td>- 3 H. pylori-negative</td>
</tr>
<tr>
<td>mean age 66 years (SD ± 6.3)</td>
</tr>
<tr>
<td>2 females, 1 male</td>
</tr>
</tbody>
</table>
5.2 Types of erosion

In the follow-up endoscopy, 38% (20/52) of the patients and 11% (7/66) of the controls had gastric erosions ($p = 0.001$; IV). The type of erosion was most often similar in both visits, but in a remarkable proportion (30%) the type had changed. (Table 5; IV). There was no significant difference in age or sex with the respect to the occurrence of erosions. (III)

Table 5. Evolution of gastric erosion types in erosion patients and controls. (IV: Table 1).

<table>
<thead>
<tr>
<th>Initial visit erosion status</th>
<th>Follow-up visit erosion status</th>
<th>Erosion any type N (%)</th>
<th>Type I N (%)</th>
<th>Type II N (%)</th>
<th>Type III N (%)</th>
<th>No erosion N (%)</th>
<th>Total N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (any type erosion)</td>
<td></td>
<td>20 (38)</td>
<td>6 (12)</td>
<td>11 (21)</td>
<td>3 (6)</td>
<td>32 (62)</td>
<td>52</td>
</tr>
<tr>
<td>Type I</td>
<td></td>
<td>6 (60)</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>1 (10)</td>
<td>4 (40)</td>
<td>10</td>
</tr>
<tr>
<td>Type II</td>
<td></td>
<td>14 (35)</td>
<td>2 (5)</td>
<td>10 (25)</td>
<td>2 (5)</td>
<td>26 (65)</td>
<td>40</td>
</tr>
<tr>
<td>Type III</td>
<td></td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100)</td>
<td>2</td>
</tr>
<tr>
<td>Controls (no erosion)</td>
<td></td>
<td>7 (11)</td>
<td>2 (3)</td>
<td>5 (8)</td>
<td>0 (0)</td>
<td>59 (89)</td>
<td>66</td>
</tr>
</tbody>
</table>

Erosion patients have been grouped according to the dominant type of erosion.

5.3 Etiological factors (I)

5.3.1 Herpes simplex virus

At the initial visit and at the follow-up, erosion patients and controls had a similar prevalence of increased antibody titres to HSV (36% vs. 23%). Erosion patients with high HSV antibody titres significantly more commonly had erosions at the follow-up endoscopy than those with low HSV antibody titres (Figure 6).

Based on this serological evidence pointing to an association between HSV and chronic/recurrent erosions, we sought evidence of an actual local HSV infection by immunohistochemical staining and PCR. Specimens from erosions taken at the follow-up visit were analysed, but no evidence for HSV was found with either immunohistochemistry or PCR, all specimens being negative.
5.3.2 Helicobacter pylori

Erosion frequency rate was not related to the presence or absence of *H. pylori* infection. At the initial visit, the *H. pylori*-positivity rate was similar in the whole erosion group (60%) and in the controls (65%; \(p = \text{NS}\)), and also among those subjects available for follow-up studies (erosion group 65%; controls 73%; \(p = \text{NS}\); Figure 3). At the follow-up visit, *H. pylori*-positive were 59% of the patients and 52% of the controls (\(p = \text{NS}\); Figure 4).

The proportion subjects with erosions at the follow-up visit were similar in *H. pylori*-positive (41%, 11/27) and -negative patients (33%, 5/15; \(p = \text{NS}\); Figure 7). Similarly, in the control group, the erosion rate at follow-up was not related to the presence (15%, 5/31) or absence of *H. pylori* (0%, 0/15; \(p = \text{NS}\)). There was no significant difference between the erosion type and *H. pylori* infection at the follow-up visit. (III).
5.3.3 Non-steroidal anti-inflammatory drug

The use of NSAIDs within one week before the initial visit was more common in the erosion group than in the control group, but at the follow-up, the rate of use was similar in both groups (Figure 8). Furthermore, there was no correlation with concurrent erosions at the follow-up visit. The use of NSAID was not related with the type of erosion. (I).
5.3.4 Simultaneous effects of Herpes simplex virus, Helicobacter pylori and non-steroidal anti-inflammatory drug

Some patients presented with several potential risk factors for the chronic/recurrent erosions. The significance of simultaneous high HSV antibody titres at the initial visit, \textit{H. pylori} infection or usage of NSAID at the follow-up visit was analysed in a pair-wise manner. However, there was no evidence for a cumulative effect on the presence of erosions at follow-up.

We compared the influence of age, sex, HSV antibody titres (initial visit), \textit{H. pylori} infection and NSAID use (preceding the follow-up visit) with the occurrence of erosions in the follow-up endoscopy in the patient group. Using logistic regression analysis, high HSV antibody titres proved to be the only statistically significant factor predicting erosions at follow-up (Table 6).
Table 6. Occurrence of erosions at the follow-up visit in patient group analysed with logistic regression (I: Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>p</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at the follow-up visit</td>
<td>0.7502</td>
<td>0.9812</td>
<td>0.87–1.10</td>
</tr>
<tr>
<td>Sex (M vs F)</td>
<td>0.8920</td>
<td>0.8884</td>
<td>0.16–4.90</td>
</tr>
<tr>
<td>Antibody titers (logarithmic value) against HSV at the initial visit</td>
<td>0.0038</td>
<td>4.8397</td>
<td>1.66–14.1</td>
</tr>
<tr>
<td>H. pylori in biopsy</td>
<td>0.4297</td>
<td>2.0765</td>
<td>0.34–12.6</td>
</tr>
<tr>
<td>NSAID used or not used within one week before the follow-up visit</td>
<td>0.6062</td>
<td>0.6516</td>
<td>0.13–3.32</td>
</tr>
</tbody>
</table>
| Constant                                     | 0.1883  | 5.3.5 Other factors and the erosion rate

There were no major changes in the erosion rate or other factors. In the patient group, gastric erosions were less frequent in those that had used sucralfate recently (0/7) before the follow-up visit compared to those not using this drug (16/35; p = 0.033). The use of alcohol, the smoking habits or the use of drugs other than NSAIDs or sucralfate did not influence the occurrence of erosions at follow-up in the patient group.

5.4 Histopathology of gastric antral erosions (II)

5.4.1 Comparison of inflammatory changes in the erosion and in the background antral mucosa

Table 7 shows a summary of the comparisons of the severity of main histopathological features in the erosion samples and in the background antral mucosa on the initial visit. An example of histopathological findings in or adjacent to the erosion and in the background antral mucosa is shown in Figure 9.

In H. pylori-positive subjects, erosion samples exhibited more epithelial degeneration (epithelial tufting) in the initial visit; an example case is presented in Figure 10. The erosion samples were awarded higher scores for numbers of neutrophils and eosinophils. On the contrary, the number of germinal centres was lower in the erosion samples than in the antral mucosa. Erosion samples showed more prominent vasodilatation on the initial visit. In H. pylori-negative subjects in the initial visit, erosion samples had higher scores for neutrophils, eosinophils, vasodilatation, foveolar hyperplasia and microscopic erosion than the antral samples. (Table 7).
Table 7. Main histological features in the initial visit samples of endoscopically visible erosion and in intact antral mucosa in *H. pylori*-positive (N = 52, except in glandular atrophy N = 28) and negative (N = 31, except in glandular atrophy N = 26).

<table>
<thead>
<tr>
<th>Histological feature</th>
<th><em>H. pylori</em>-positive subjects</th>
<th><em>H. pylori</em>-negative subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Erosion Antrum p</td>
<td>Erosion Antrum p</td>
</tr>
<tr>
<td></td>
<td>Mean SD Mean SD</td>
<td>Mean SD Mean SD</td>
</tr>
<tr>
<td>Epithelial alterations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tufting</td>
<td>19 25 10 20 0.002</td>
<td>0.8 2.3 0.2 0.9 NS</td>
</tr>
<tr>
<td>Foveolar score</td>
<td>1.1 0.6 1.2 0.6 NS</td>
<td>1.3 0.6 0.8 0.6 0.007</td>
</tr>
<tr>
<td>Glandular atrophy</td>
<td>0.9 0.7 1.0 0.7 NS</td>
<td>0.2 0.5 0.2 0.4 NS</td>
</tr>
<tr>
<td>Intestinal metaplasia</td>
<td>3.9 14 4.0 12 NS</td>
<td>0.7 2.5 0.2 0.9 NS</td>
</tr>
<tr>
<td>Inflammatory cell reaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>1.9 1.0 1.2 0.9 0.000</td>
<td>0.3 0.8 0.1 0.3 0.023</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1.6 0.8 1.1 0.8 0.000</td>
<td>1.0 1.0 0.3 0.6 0.005</td>
</tr>
<tr>
<td>Monon. infl. cells</td>
<td>2.1 0.7 2.0 0.7 NS</td>
<td>0.6 0.9 0.5 0.6 NS</td>
</tr>
<tr>
<td>Germinal centres</td>
<td>0.00 0.0 0.04 0.1 0.038</td>
<td>0.00 0.0 0.00 0.0 NS</td>
</tr>
<tr>
<td>Stromal changes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrosis</td>
<td>0.8 0.7 0.7 0.6 NS</td>
<td>1.5 0.7 1.3 0.7 NS</td>
</tr>
<tr>
<td>Vasodilatation</td>
<td>0.6 0.5 0.2 0.5 0.008</td>
<td>1.0 0.8 0.4 0.6 0.001</td>
</tr>
</tbody>
</table>

Figures indicate mean scores except for epithelial tufting and intestinal metaplasia where mean extent (%) is indicated. Differences between erosion and antral samples were compared with Wilcoxon Signed Rank Test. Statistical comparison of *H. pylori*-negative and -positive subjects is described in the text.
Fig. 9. Photomicrographs of antral mucosa immediately adjacent to chronic/recurrent erosion (A) and non-eroded antral mucosa (B) of the same *H. pylori*-positive patient, who had recently used an NSAID. Infiltration of neutrophilic leukocytes is more abundant in the erosion sample (A) than in non-eroded antral mucosa (B). Reference line is 0.1 millimeters. Hematoxylin-Eosin staining. (II: Fig 2).

Fig. 10. Photomicrograph of epithelial tufting in antral mucosa of a *H. pylori*-positive patient (A). Another *H. pylori*-positive patient, but without evidence of epithelial tufting (B). Reference line is 0.1 millimetres. Hematoxylin-Eosin staining.

At the initial visit, there was a correlation between the erosion and the background mucosa samples in the intensity of inflammation and in the severity
of epithelial degeneration in both \( H. \text{pylori} \)-negative and positive patients. (Spearman rank correlation, data not shown).

5.4.2 Role of \textit{Helicobacter pylori} on histopathology of erosions

On both visits, the erosions of the \( H. \text{pylori} \)-positive subjects showed significantly stronger intensity of inflammation compared to \( H. \text{pylori} \)-negative subjects, and on the initial visit, they also had significantly more severe epithelial degeneration, while \( H. \text{pylori} \)-negative subjects displayed significantly clearer stromal changes (Table 7).

5.4.3 Role of non-steroidal anti-inflammatory drugs on the histopathology of erosions

Those \( H. \text{pylori} \)-positive patients that had recently used NSAIDs, had a significantly higher score of neutrophils in their erosion samples compared to those who had not used these drugs at the initial visit (Figure 11).

At the initial visit, those \( H. \text{pylori} \)-negative patients that had recently used NSAIDs had a lower score (0.8; \( N = 12 \)) of foveolar hyperplasia in the erosion samples compared to non-NSAID users (1.5; \( N = 16 \); \( p = 0.015 \)). At the initial visit, \( H. \text{pylori} \)-positive subjects that had recently used NSAIDs, displayed a greater difference (-0.7; \( N = 10 \)) in the grade of atrophy between the erosion sample and antral mucosa than those who had not recently used NSAIDs (-0.2; \( N = 18 \); \( p = 0.010 \)).
5.4.4 Role of Herpes simplex seropositivity on the histopathology of erosions

At the initial visit among *H. pylori*-positives, patients with high levels of HSV antibodies exhibited a higher score of neutrophils in the erosion samples than those patients with a low titre of these antibodies (Figure 12). A similar trend was seen in the background mucosa (Figure 12). No such difference emerged at the follow-up visit, probably due to the small number of cases (data not shown).
5.4.5 Relationship of histopathological features in erosions and the chronicity/recurrence of the erosions

In the *H. pylori*-positive patients, a high degree of active inflammation in the erosion sample predicted chronicity/recurrence of the erosions (Figure 13). In *H. pylori*-negative subjects, histopathological features did not display any predictive value.

5.4.6 Histopathological features in erosions and the risk for the development of peptic ulcer or gastric malignancy

At the initial visit, no single significant difference emerged in the histopathology that would have identified those patients who would develop peptic ulcer.

No intraepithelial neoplastic changes were present in the initial visit erosion biopsies.
Fig. 13. Neutrophil scores in the erosion samples and in the background antral mucosa in patients with non-chronic/non-recurrent (erosion in the initial visit only) and chronic/recurrent (erosion at both visits) erosions in *Helicobacter pylori*-infected patients. Mean score (box) and standard deviation (thin bar) are shown. (II: Fig. 3).

5.5 Progression of gastritis in patients with gastric erosions (III)

Main features of gastritis and their evolution in the erosion group and in the controls are summarized in Tables 8 and 9.
Table 8. Main histological features in the antral mucosa in erosion patients and controls in the initial and the follow-up visit about 17 years later. Statistical comparison is described in detail in the text. (III: Table I).

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Helicobacter pylori positive</th>
<th>Helicobacter pylori negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Atrophy†</td>
<td>0.8(0.8)</td>
<td>1.1(0.6)</td>
</tr>
<tr>
<td></td>
<td>0.3(0.5)</td>
<td>0.2(0.4)</td>
</tr>
<tr>
<td>Gastritis†</td>
<td>1.9(0.7)</td>
<td>2.4(0.8)</td>
</tr>
<tr>
<td></td>
<td>0.6(0.6)</td>
<td>0.4(0.6)</td>
</tr>
<tr>
<td>Activity†</td>
<td>1.3(0.9)</td>
<td>1.6(0.8)</td>
</tr>
<tr>
<td></td>
<td>0.0(0.0)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Intestinal metaplasia‡</td>
<td>3(11)</td>
<td>6(23)</td>
</tr>
<tr>
<td></td>
<td>2(14)</td>
<td>2(13)</td>
</tr>
<tr>
<td>Microscopic erosion‡</td>
<td>5(19)</td>
<td>7(27)</td>
</tr>
<tr>
<td></td>
<td>0(0)</td>
<td>1(7)</td>
</tr>
<tr>
<td>Tufting‡</td>
<td>11(41)</td>
<td>8(31)</td>
</tr>
<tr>
<td></td>
<td>1(7)</td>
<td>1(7)</td>
</tr>
</tbody>
</table>

† Mean and standard deviation (in parentheses)
‡ The number of cases showing the abnormality (percent in parentheses)

Table 9. Main histological features in the body mucosa in erosion patients and controls in the initial and the follow-up visit about 17 years later. Statistical comparison is described in detail in the text. (III: Table II).

<table>
<thead>
<tr>
<th>Histological feature</th>
<th>Helicobacter pylori positive</th>
<th>Helicobacter pylori negative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients</td>
<td>Controls</td>
</tr>
<tr>
<td>Atrophy†</td>
<td>0.1(0.3)</td>
<td>0.4(0.6)</td>
</tr>
<tr>
<td></td>
<td>0.6(1.3)</td>
<td>0.6(1.2)</td>
</tr>
<tr>
<td>Gastritis†</td>
<td>1.8(0.6)</td>
<td>1.9(0.8)</td>
</tr>
<tr>
<td></td>
<td>0.8(0.9)</td>
<td>0.5(0.8)</td>
</tr>
<tr>
<td>Activity†</td>
<td>0.6(0.7)</td>
<td>0.7(0.8)</td>
</tr>
<tr>
<td></td>
<td>0.1(0.3)</td>
<td>0.0(0.0)</td>
</tr>
<tr>
<td>Intestinal metaplasia‡</td>
<td>0(0)</td>
<td>1(4)</td>
</tr>
<tr>
<td></td>
<td>2(14)</td>
<td>3(20)</td>
</tr>
<tr>
<td>Microscopic erosion‡</td>
<td>1(4)</td>
<td>1(4)</td>
</tr>
<tr>
<td></td>
<td>1(7)</td>
<td>0(0)</td>
</tr>
<tr>
<td>Tufting‡</td>
<td>7(29)</td>
<td>5(9)</td>
</tr>
<tr>
<td></td>
<td>0(0)</td>
<td>0(0)</td>
</tr>
</tbody>
</table>

† Mean and standard deviation (in parentheses)
‡ The number of cases showing the abnormality (percent in parentheses)

5.5.1 Severity of chronic gastritis

In the H. pylori-positive subjects, the severity of gastritis (scores of mononuclear cells) was similar in erosion patients and controls in the initial visit (Tables 8 and 9). At the follow-up visit, the severity had increased in the antral mucosa in the patient group (erosion at the initial visit) and in the body in the controls, but no
significant differences were detected between the groups. In H. pylori-negative subjects, the amount of mononuclear cells of gastric mucosa was low on both visits. (Figure 14).

Fig. 14. Evolution of chronic gastritis in erosion patients (double lines) and controls (single lines). Mean degree of chronic gastritis at the initial visit and after nearly 20 years' of follow-up. (III: Fig. 2).

5.5.2 Activity of gastritis

In the body mucosa, no dynamic activity changes developed, but in the antrum there was a trend towards more neutrophils in patients compared to controls, among H. pylori-infected subjects.

On the initial visit if one considered only the H. pylori-positive subjects, then the patients showed a lower score (0.56 ± 0.65) for neutrophilic leucocytes in the body mucosa than controls (1.07 ± 0.91; p = 0.035). Initially, there were no significant differences in the antral mucosa. At the follow-up visit, activity displayed a non-significant increase in the patient group, while the controls showed a non-significant decrease. These changes resulted in a trend toward patients having more neutrophils in the antrum (1.58 ± 0.76) compared to controls (1.19 ± 0.83; p = 0.060). In H. pylori-negative subjects, the gastric mucosal neutrophils were largely absent and displayed no temporal changes. (Table 8 and 9; Figure 15).
5.5.3 Atrophic changes, intestinal metaplasia and dysplasia

*H. pylori*-infected patients showed less inflammation in body mucosa compared to controls, and a trend toward less atrophy in the body. Some intestinal metaplasia appeared only in *H. pylori*-infected controls, but not in patients. Intraepithelial neoplasia – all mild and of the intestinal metaplasia type – was a rarity.

On the initial visit, the grade of atrophy in *H. pylori* infected subjects did not show any significant differences between patients and controls. Different erosion types did not reveal any significant differences in any histological parameters of gastritis (data not shown). At the follow-up visit, antral mucosa showed no significant changes in the degree of atrophy, but body mucosa displayed an increase, which was more evident in the control group ($p = 0.002$). Accordingly, at the follow-up visit, controls showed more severe atrophy than patients ($p = 0.079$). In *H. pylori*-negative subjects, the atrophic changes in the antrum had been almost absent in the initial visit and remained low during follow-up. However, even in the *H. pylori*-negative group, occasional subjects showed atrophic changes in the corpus mucosa. (Tables 8 and 9; Figure 16).
At the initial visit, there were no significant differences in prevalence of intestinal metaplasia between patients and controls. At follow-up, *H. pylori*-positive controls showed an increase in the extent of intestinal metaplasia both in the antrum (mean % ± SD from 1.4 % ± 7.4 to 7.4 % ± 15.4; *p* = 0.005) and the body (from 0.7 % ± 3.7 to 4.5 % ± 10.3; *p* = 0.007). In the patient group, no significant changes were seen. At the follow-up visit, *H. pylori*-positive controls showed more prevalent intestinal metaplasia in the body mucosa than patients (*p* = 0.014). In *H. pylori*-negative subjects, no significant differences emerged. (Tables 8 and 9).

At the initial visit, only one patient showed intraepithelial neoplasia in the intestinal metaplastic epithelium, but none of controls. At the follow-up visit, intraepithelial neoplasia was found in two patients and in one control (*p* = NS). In all cases, intraepithelial neoplasia was graded as being mild.

### 5.5.4 Microscopic erosions and epithelial reactive changes

The presence of microscopic erosions was assessed in both antral and body biopsies taken outside endoscopically visible erosions.

At the initial visit, the presence or score of microscopic erosions did not differ significantly between the groups. In addition, there was no significant
evolution in either group. However, in the follow-up visit, *H. pylori*-positive controls showed a higher prevalence and higher score for microscopic erosions in the body mucosa ($p = 0.012$; Figure 17), while patients showed higher figures than controls in the antral mucosa (score $0.42 \pm 0.86$ vs. $0.10 \pm 0.30$; $p = 0.079$). Epithelial tufting exhibited a similar pattern, a significant difference between patients and controls, emerging at the follow-up visit in the body mucosa. Among *H. pylori*-positive subjects, patients showed a lower prevalence ($p = 0.007$) and less extensive epithelial tufting ($1.7 \pm 4.4$ vs. $10.5 \pm 14.6$; $p = 0.002$) than controls. At both visits, both microscopic erosions and epithelial tufting were rare and there were no significant differences between the groups in *H. pylori*-negative subjects. (Tables 8 and 9).

![Fig. 17. Evolution of microscopic erosions in the corpus mucosa in patients (double lines) and controls (single lines). Mean degree of microscopic erosions at the initial visit and after nearly 20 years' of follow-up. (III: Fig. 4).](image)

**5.5.5 Non-steroidal anti-inflammatory drug use and features of gastritis**

Recent use of NSAID before the initial visit had no effect on any severity parameters assessing gastritis, in *H. pylori*-positive or negative subjects in either of the groups.
5.5.6 Parietal cell antibodies

Among the \textit{H. pylori}-positives, controls possessed more often parietal cell antibodies (23\%; 7/31) than patients (0\%; 0/26; \( p = 0.01 \)). In \textit{H. pylori}-negatives, parietal cell antibodies were detected in 31\% (4/13) of controls and in 7\% (1/15; \( p = \text{NS} \)) of patients.

5.5.7 Ulcer development during the follow-up

In patients with an ulcer or scar, the activity of gastritis in the antrum increased from 1.33 to 1.88 (\( p = 0.034 \)), and also chronic gastritis showed a trend towards an increase (from 1.78 to 2.50; \( p = 0.063 \)).

5.6 Clinical features, ulcer and malignancy

5.6.1 Endoscopical findings

At the follow-up visit, the patients were more likely to show signs of an active peptic ulcer or the scar of a healed peptic ulcer (17\%; 9/52) than the controls (5\%; 3/66; \( p = 0.031 \)). Among the \textit{H. pylori}-positive subjects, the risk was significantly higher in the patient group than in the controls (Figure 18). Patients and controls exhibited no other significant differences concerning other endoscopic findings (IV: Table 2). At the follow-up visit, most patients with concurrent ulcer or scar had recently used NSAIDs (67\%, 6/9), whereas for those controls with concurrent ulcer or scar, two of three were \textit{H. pylori}-positive and one of three had recently used NSAID.

5.6.2 Symptoms and other clinical data

At the initial visit, the patients showed more common upper abdominal pain (100\%; 54/54) than the controls (91\%; 64/70; \( p = 0.035 \)). At the follow-up visit, the patients and the controls showed equal frequencies (70\%) of dyspepsia or upper abdominal pain (patients 37/53; controls 49/70). At the follow-up, the presence or type of erosions showed no relationship with symptoms.
Among the *H. pylori*-infected patients, those who recently had used an NSAID before follow-up visit, 54% (7/13) had motility type dyspepsia, while only 8% (1/12) of those who had not recently used an NSAID, showed this type of dyspepsia (*p* = 0.03).

![Fig. 18. Ulcer risk at follow-up visit in the patient and the control groups in originally *H. pylori*-negatives and -positives.](image)

On both visits no significant differences emerged between the patients and the controls in laboratory parameters, or between the subjects with or without current erosion at the follow-up-visit.

### 5.6.3 Surgical operations and other diseases

In all, showed 6% (3/54) of the patient group had undergone gastric surgery, whereas only one individual (1%, 1 of 69) in the control group had required this kind of surgical treatment (*p* = NS). One fatal haemorrhage due to a gastric ulcer
occurred in the control group, but none in the patient group. The patient group suffered less often from rheumatoid arthritis (0%; 0/54) than the control group (10%; 7/69; p = 0.018), but none of these individuals showed sings of erosions at the follow-up visit. No other significant differences were noted in the incidence of other diseases. No significant differences emerged between the groups regarding diseases in close relatives.

5.6.4 Occurrence of malignancies, mortality, and causes of death

The patient group showed a significantly lower incidence of malignancy (5%; 6/117) than the controls (15%; 17/117) during the 16 years of follow-up (p = 0.0247). During the follow-up, in the patient group there were three cases of lung cancer, one of kidney cancer and one of prostate cancer, and a simultaneous case with a gastric carcinoid tumour and an oesophageal cancer. In the control group, there were four cases of breast cancer, three rectal, two uterine, one gastric, one lung, one ovarian, one prostate, one kidney, one skin and one central nervous system cancer, and one unspecified carcinoma. The incidence of malignancy was not influenced by smoking habits.

During the 16 years of follow-up, no significant differences emerged in the mortality (19%; 22 of 117 of the patients and 22%; 26 of 117 of the controls; p = NS). Two deaths in the patient group (9%) and six deaths (23%) in the control group were caused by malignancy (p = NS). One death occurred due to GI haemorrhage in the control group.
6 Discussion

This is the first long-term follow-up study addressing the clinical significance and pathology of gastric erosions. Nearly twenty years of follow-up revealed that the erosions are chronic or recurrent in more than one third of the cases. The current study also demonstrates that there is a significant association between increased HSV antibody titres and gastric erosions - especially with chronic or recurrent erosions. This suggests that a significant proportion of chronic gastric erosions is related to HSV infection. In *H. pylori*-positive patients, this study also supports the importance of *H. pylori* and gastric acid in the pathogenesis of chronic/recurrent gastric erosions. In addition, focally enhanced inflammation, perhaps evoked by HSV infection or NSAID use, may be important in the pathogenesis. Active inflammation in the erosions predicted their chronicity or recurrence, as did the high HSV antibody titres. In addition, in *H. pylori*-positive subjects with gastric erosions, this study observed that gastritis shows an evolution towards antral predominance, whereas a body predominance, including the development of atrophic changes, is rare. Accordingly, *H. pylori*-positive patients with erosions display the characteristics of gastritis of the duodenal ulcer phenotype. Finally, chronic or recurrent erosions are mostly without serious complications. However, *H. pylori*-positive patients with erosions are at a significant risk of developing peptic ulcer, highlighting the benefits of eradication therapy.

6.1 Methodological aspects

We succeeded, despite the very long follow-up time, to persuade half of the subjects to come to the follow-up visit. Such a long follow-up time in originally middle-aged subjects results in a high amount of diseases and marked mortality rate.

Patients may not remember past symptoms over such a long time and this may influence the results. For example, the use of medications, eradication treatment against *H. pylori* – may be forgotten during the long follow-up period.

Only a few experienced endoscopists participated in this study. The same endoscopist examined a marked proportion of the same patients on both visits. The endoscopy systems have also developed substantially from fiberoptic systems to video based systems, and a more precise description can now be done. It
remains undecided, whether these kinds of methodological development have affected the erosion detection rate.

The histological samples were not similarly representative in the late seventies as compared with the nineties. The number of sampling containers, specimen size, and the preparation of samples have changed during that time. However, with re-examination of samples, it was possible to use modern criteria of examination for both visits. The reproducibility of histological grading of the inflammation between pathologists is not excellent (Talebkhan et al. 2009). Furthermore, $\kappa$ values between pathologists classifying gastric mucosa atrophy have been reported to vary from poor (0.37) to excellent (Rugge et al. 2002). To avoid this bias, the same experienced pathologist reanalysed all samples.

If erosions were detected again after 19 years either they are chronic – that is they are present all the time – or recurrent, i.e. they exist now and then. It is not possible to draw any conclusions about this by assessing the location of erosions due to their small size and multiplicity. Peptic ulcer is recurrent disease and the same is the case with erosions. Perhaps erosions should be perceived as a condition, in which there is an underlying predisposition towards having erosions. Thus erosions may not always be present at any given moment, but because of some underlying predisposition, they may reappear at other times.

It was possible to re-endoscope 44% (52 of 117) patients and 57% (67 of 117) controls. Aging and chronic diseases in the study persons were probably major reasons to explain why some subjects were unable to attend the study, and in addition, there were several deaths prior to the planned follow-up visit. Patients, who had changed their *H. pylori* status between visits, would have complicated the study, and in addition, there were some persons receiving anticoagulation therapy, which were two other reasons, which reduced the final study groups to 36% (42 of 117) and 39% (46 of 117) respectively.

### 6.2 Aetiology and pathogenesis of chronic/recurrent gastric erosions

The aetiology of gastric erosions seems to be multifactorial and a complete understanding of the various contributing factors as well as their interactions and mechanisms are largely unknown. Both chemicals, such as use of NSAIDs or alcohol or cigarette smoking, and diseases, including *H. pylori* and HSV infections and diseases leading to hyperacidity, might be involved in the pathogenesis of this disorder (Bernersen et al. 1992, Karvonen & Lehtola 1983,
Long lasting follow-up studies, which would evaluate the relationship of these factors with chronic/recurrent gastric erosions, are lacking. One of the strengths of this study is that half of 234 subjects from the original cohort could be examined after a mean follow-up of almost 20 years.

Exclusively high titres of antibodies against HSV exhibited a significant association with chronic/recurrent gastric erosions. This suggests that HSV may be at least part of the reason for a subset of gastric erosions and furthermore that these erosions may, as a consequence, become chronic or recurrent. However, immunohistochemistry and PCR of erosion biopsies failed to reveal any HSV antigen or DNA. One must ask the question, what is the reason for this contradiction? The most obvious explanation is that HSV is not present in the erosion itself, as demonstrated here, but may reside in the submucosal ganglia but still cause mucosal defects (Gesser et al. 1995). Therefore, specimens representing the entire thickness of the gastric wall might be necessary to further analyse the relationship between HSV and gastric erosions.

The role of HSV in the pathogenesis of gastroduodenal ulcers is still unclear. Molecular biological methods have detected HSV DNA in a minority (less than 10%) of gastroduodenal ulcers (Kemker et al. 1992). The results of HSV serology in peptic ulcer are not convincing (Archimandritis et al. 1992, Kottaridis et al. 1989). Oral inoculation with HSV-1 induced multiple gastric ulcers in about half of animals in an immunodeficient mice model. In this study, the viral antigen was rarely found in the ulcer, but in all ulcers located near to the virus-infected ganglia, suggesting that the mucosal defects are related to the HSV infection (Gesser et al. 1995). HSV-1 is commonly first encountered during childhood as an oral infection, but after this primary infection has resolved, the virus usually stays in a latent form within the neural ganglia, to be activated later in some patients (Gesser & Koo 1996).

*H. pylori*-positive patients with high HSV antibody titres had higher neutrophil scores in the erosion samples than patients with low titres. However, the high HSV antibody titres were not significantly associated with the intensity of inflammation in the background antral mucosa. This suggests that HSV infection associates with focally enhanced inflammation in the antral mucosa.

In the follow-up examination, the presence of *H. pylori* infection was not significantly associated with the presence of gastric erosions. The current study does not support the theory that *H. pylori* plays a crucial role in the pathogenesis
of chronic gastric erosions. However, the exclusion of the ulcer patients from the study may have caused exclusions of some erosions possibly caused by *H. pylori*.

Another important factor in the pathogenesis of gastric erosions is thought to be the use of NSAIDs (O’Laughlin et al. 1981). Erosions were to some extent associated with the use of NSAIDs. Recent use of NSAIDs was significantly more common in patients with erosions than in controls at the initial visit, but at the follow-up visit, the use of NSAIDs did not associate with erosions. NSAIDs may cause acute or subacute erosions, even symptomatic erosions, leading to a need for a diagnostic gastroscopy, as was the case in patients before the initial gastroscopy in the current study (O’Laughlin et al. 1981). This injurious effect might diminish after long-term use of NSAID (Graham et al. 1983).

The results of the current study do not support the hypothesis that *H. pylori* or HSV infection can influence the occurrence of NSAID associated gastric erosions. In patients using NSAIDs, the significance of *H. pylori* infection is controversial. It has been reported that *H. pylori*-positive patients using NSAID may develop erosions and ulcers more often than *H. pylori*-negative patients (Taha et al. 1995). However, in other studies examining patients using NSAIDs, erosive lesions in the gastric mucosa were less common in *H. pylori*-positive patients than in *H. pylori*-negative individuals (Graham et al. 1991, Hart et al. 2010). One possible protective mechanism is the induction of prostaglandin synthesis in response to *H. pylori* infection. In addition, *H. pylori* infection can lead to loss of parietal cells and the stomach will become less acidic. Gastric acid itself has been reported to be an essential factor in NSAID induced gastric erosions. (Elliott et al. 1996, Hart et al. 2010, Hudson et al. 1993).

In the current study, significantly less foveolar hyperplasia was observed in the erosions of NSAID users in *H. pylori*-negative patients, i.e. the regenerative capacity of the epithelium might have been suppressed by these drugs (Leung et al. 2000). This is supported by another finding in which NSAID associated gastric ulcer patients had more often moderate/severe foveolar hyperplasia than *H. pylori*-infected controls without ulcers (Haber & Lopez 1999).

In conclusion, a significant association was found between the increase in the HSV antibody titres and gastric erosions, and with chronic or recurrent erosions. In contrast, *H. pylori* infection, use of NSAID or alcohol did not show any apparent associations with chronicity. According to these observations, HSV infection may be responsible for a substantial proportion of chronic/recurrent gastric erosions. In order to clarify the role of local HSV infection, further studies should be performed to confirm the topographical association of mucosal defects
and HSV virus in the nervous ganglia of the gastric wall. Antiviral treatment trials may also provide useful information.

6.3 Histopathology of chronic/recurrent gastric erosions

The observations in the current study indicate that in H. pylori-positive subjects there is more active inflammation in the biopsies of erosions than in the background antral mucosa. In H. pylori-positive subjects, both a high antibody level to HSV and the use of NSAIDs were linked with this focally enhanced inflammation. Stromal changes were a characteristic found in the erosion samples from H. pylori-negative patients. In H. pylori-positive subjects, the presence of highly active inflammation in erosions seemed to pose a risk of chronicity or recurrence of erosions after 19 years. These findings may help in understanding the pathogenesis of gastric erosions and in identifying factors affecting their prognosis.

A positive correlation in the intensity of inflammation was observed between erosion and the surrounding mucosa. This suggests that well-known factors affecting the intensity of gastritis, such as polymorphisms in the host genes regulating the mucosal immune system and the virulence of H. pylori strain, can similarly influence the extent of inflammation in the erosions and the surrounding mucosa (Koivurova et al. 2003, Suerbaum & Josenhans 2007). These factors still do not explain the observation that there was a difference between the inflammation activity at the erosion and in the surrounding mucosa. Two potential mechanisms exist that could explain why more severe inflammation occurred in the mucosa of erosion samples than in the surrounding mucosa. First, during the development of the erosion, the local inflammatory response is secondarily enhanced by the response to tissue destruction (Tarnawski 2005). Second, there could be pre-existing structural or functional abnormalities present at the site of erosion, even before the development of the erosion, which either evoke intense local inflammation or become manifest in their own right.

In the erosion samples of H. pylori-positive patients, high HSV antibody titres were associated with higher neutrophil scores than patients with low titres, but no such difference was seen in the background antral mucosa. Accordingly, HSV infection seems to associate with focally enhanced inflammation in the antral mucosa. One possible explanation is that infection of autonomic ganglia interferes with the mucosal innervation, and, then due to insufficient anti-inflammatory neural signalling, this evokes intense focal inflammation and then
erosion (Borovikova et al. 2000, Croen et al. 1987, Gallowitsch-Puerta & Pavlov 2007, Gesser & Koo 1997). This is speculative, as the presence of a ganglial HSV infection was not studied in the current study.

In the erosion samples in *H. pylori*-positive patients, NSAID users had more intensive infiltration of neutrophils compared to nonusers. This indicates that the use of an NSAID may worsen pre-existent inflammation and supports the importance of neutrophils in the development NSAID related gastric lesions (Wallace et al. 1990). In *H. pylori*-negative patients, NSAID users showed significantly less foveolar hyperplasia in the erosions than nonusers, i.e. these drugs might suppress the regenerative capacity of the epithelium (Leung et al. 2000).

At the initial visit, *H. pylori*-positive patients, chronic/recurrent antral erosions showed higher scores of neutrophils compared to non-chronic/non-recurrent erosions. This suggests that highly active inflammation in the erosion either predisposes an individual to recurrence or impedes healing of the erosions.

In conclusion, antral erosions with strong neutrophilic reaction associate with a tendency for chronicity/recurrence. This study revealed that the use of NSAIDs and seropositivity for HSV are associated with focally highly active inflammation in the region of erosion in *H. pylori*-positive subjects. This supports the role of these factors in the pathogenesis of gastric erosions, emphasizing the importance of local regulation of inflammation and the role of neutrophils in the pathogenetic cascade leading to erosions.

### 6.4 Progression of gastritis in patients with chronic or recurrent gastric erosions

In patients with and without gastric erosions, the cross-sectional and longitudinal results indicate that the features and evolution of gastritis are different. The main factor affecting gastric histology in both the cross-sectional and dynamic respects was *H. pylori* infection. In *H. pylori*-negative subjects chronic gastritis was absent in most cases regardless of the erosion status, and there was no association with NSAID use or histological reactive gastritis.

In *H. pylori*-positive erosion patients, the body mucosa initially showed some features indicative of less intensive inflammation than controls. These patients showed a trend towards a lower degree of atrophy and significantly fewer neutrophilic leucocytes in the body than controls. Miyake *et al.* (2005) found that the mean activity score of the corpus was significantly higher in those ulcer
patients that developed gastric erosion after *H. pylori* eradication compared to those who did not develop erosion. In the current study, patients with erosion and controls exhibited no significant differences in activity score of the corpus in those, which developed gastric erosion at the follow-up visit (data not shown). Stolte et al. (1999) examined *H. pylori*-infected subjects and noted that patients with complete erosion show more active and severe antral gastritis than subjects without erosions, while no differences were seen in the body mucosa. These findings in subjects with gastric erosions are in agreement with the results of Stolte et al. in pointing to the importance of antral predominance of *H. pylori* gastritis, although the current study did not detect significant differences in the antral mucosa.

The evolution of gastritis revealed differences, with the severity of antral gastritis increasing in the erosion patients, and body gastritis with atrophic changes in the controls. In subjects with erosions, these differences could be related to the low prevalence of autoimmune-mediated gastric body destruction, as shown by the infrequent occurrence of parietal cell antibodies.

The clinical importance of the topographic types of gastritis lies in the pattern of complications associated with each type as shown by previous studies (Sipponen 2001). Atrophy and other features of inflammation are associated with each pattern and this may have prognostic significance. Accordingly, antrum predominant gastritis is associated with the risk of peptic ulcer disease and antral atrophy, and in addition, intestinal metaplasia and more severe activity in the antrum compared to body mucosa (Sipponen 2001). This pattern of antral gastritis reveals marked degenerative and regenerative alterations in the surface epithelium (Sipponen 2001). In patients with duodenal ulcer, follow-up studies have shown that this antral predominant pattern can remain stable for up to 32 years without the development of body atrophy (Valle et al. 1996). On the other hand, patients with gastric ulcer are suffering from a more progressive form of body gastritis than non-ulcer subjects (Valle et al. 1996). It has been estimated that the prevalence of body atrophic gastritis shows an annual increase of about 1 to 3% (Correa et al. 1990, Ihamäki et al. 1985, Kuipers et al. 1995, Villako et al. 1991).

In *H. pylori*-positive patients with gastric erosions, the pattern and dynamics of gastritis share several features in common with the antrum predominant gastritis associated with the peptic ulcer risk described in other studies (Sipponen 2001, Valle et al. 1996). At follow-up, 17% of the subjects in the erosion group had peptic ulcer or scar, all being *H. pylori*-positive. Originally, the features of gastritis in this subgroup that developed ulcer did not differ from other patients
with erosions, but during the follow-up, an increase in the activity of antrum gastritis was seen. This suggests that in this subgroup the evolution of gastritis is even more antrum predominant than in erosion patients that do not develop ulcer.

The reasons for the variation in outcomes of *H. pylori* infection are not clear. Differences in the genetically determined host response, such as interleukin-1 polymorphism, and virulence of *H. pylori* strain might be factors that determine why some individuals infected with *H. pylori* develop gastric cancer or duodenal ulcer, while others do not (Blaser *et al.* 1995, El-Omar *et al.* 2000, Garcia-Gonzalez *et al.* 2001, Nomura *et al.* 2002). Based on morphological and immunological observations of gastritis in *H. pylori*-positive patients observed in this study, those genotypes that associate with body-predominant gastritis might protect from erosions. Since erosive oesophagitis in *H. pylori*-negative subjects has been associated with the same pro-inflammatory genotypes as those associated with body predominant gastritis, similar genotypes might be involved in promoting erosions in *H. pylori*-negative subjects (Koivurova *et al.* 2003).

The detailed pathogenesis of endoscopically visible erosions has not been clarified. Evidence for epithelial defects and degeneration outside of endoscopic erosions, such as microscopic erosions seen as single-cell dropouts in biopsy specimen and epithelial cell tufting, could associate with the endoscopically visible erosions in the same gastric region (Chan *et al.* 1991, Leung *et al.* 1992). Most macroscopic erosions were located in the antral mucosa, but the occurrence and extent of microscopic erosions or epithelial tufting did not associate with the presence of endoscopically visible erosions. In addition, both epithelial tufting and microerosions in the body mucosa were more abundant in the controls than in patients with erosions. Altogether, this suggests that microerosions and epithelial tufting are more related to the topographic type of *H. pylori* gastritis than to the development of erosions.

This study provides evidence for the importance of the topographic phenotype of *H. pylori*-associated gastritis in the development of gastric erosions. In addition, the development of an autoimmune reaction against body mucosa and the development of atrophic changes associate with a low prevalence of erosions. These findings pointing to the importance of gastric acid secretion are in agreement with reports indicating that after eradication of *H. pylori*, the increased risk of gastric erosions can be controlled by acid suppression therapy (Miyake *et al.* 2002).

In conclusion, the current study indicates that *H. pylori*-positive subjects with gastric erosion exhibit dynamic characteristics of gastritis of duodenal ulcer
phenotype and that the development of body predominant gastritis is rare. This highlights the importance of *H. pylori* infection and acid in the pathogenesis of gastric erosions in *H. pylori*-positive patients. Histological gastritis was virtually absent in *H. pylori*-negative patients with gastric erosions, and other pathogenetic factors need to be considered.

### 6.5 Clinical outcome of patients with gastric erosion

The results of nearly twenty years of follow-up show that in more than one third of the cases, erosions are chronic or recurrent, and peptic ulcers develop in about every sixth patient with erosions. Apart from the increased peptic ulcer risk in erosion patients infected with *H. pylori*, gastric erosions do not seem to be associated with an increased risk of local complications or other types of morbidity as compared to dyspeptic patients without erosions. Therefore, these results support the view that gastric erosions are often chronic or recurrent, but nonetheless a clinically harmless condition, except for the significantly elevated risk of peptic ulcer disease.

The finding of the high prevalence of persistent or recurrent erosions is in agreement with previous follow-up studies of shorter duration. One publication with about a six-year follow-up stated that erosions were detectable in 34% of cases (Karvonen & Lehtola 1984).

Bleeding is an important complication of gastric erosions (Laine & Weinstein 1988, Silverstein *et al.* 1981). In this study, erosion patients reported no clinical history of GI bleeding during the follow-up. In addition, no differences between the groups, or between patients with and without concurrent erosion were seen in blood haemoglobin concentrations at the follow-up visit, indicating that clinically significant bleeding is rare. However, no subjects with haemorrhagic erosions (type III) were available for follow-up, and these individuals are possibly more prone to bleed significantly, and the long-term outcome of these types of lesions remains unknown. Furthermore, without constant monitoring for occult faecal blood, the occurrence of slight or temporary bleeding cannot be excluded.

The type of erosion seems to be rather stable, as about 70% of erosions presented with the original type erosion. The erosion type had changed in about 30% of the cases, but the number of cases is too small to allow a proper analysis of evolutionary sequences. The type of erosions changed in only about 5% of cases in an earlier follow-up for a maximum of six years (Karvonen & Lehtola 1984).
None of subjects in this study had peptic ulcer at the initial visit; this was one of the exclusion criteria. At the follow-up, 17% (9/52) of patients in the erosion group had developed an active ulcer or scar. They were all *H. pylori*-positive and most (67%; 6/9) had recently used NSAID medications. This suggests that erosions, especially in *H. pylori*-positive patients or in patients using NSAIDs, are associated with a significant risk of peptic ulcer. The presence of erosions showed no significant association with *H. pylori* infection, and this seemed to indicate that *H. pylori* does not play any major role in the pathogenesis of chronic or recurrent gastric erosions. However, erosion patients presenting with concurrent peptic ulcer disease were initially excluded and this may have caused exclusion of the kinds of erosions which are with more evidently associated etiologically with *H. pylori*. Another factor explaining the absence of any association with *H. pylori* might be the high prevalence of this infection and in this respect there was no difference between the groups, which is likely related to the high prevalence of infection in the Finnish population almost 30 years ago (Kosunen *et al.* 1997). As the prevalence of *H. pylori* ulcers has become less common, the NSAID-induced ulcers have become proportionally more common. Nonetheless, the results of the current study favour eradication of *H. pylori* in patients with gastric erosions.

Four subjects (two patients and two controls) that originally were categorised as *H. pylori*-negative, converted to being positive during the follow-up. This *H. pylori* finding may have been a false negative in the initial visit, or new, true infection finding in the follow-up visit. A false negative finding can be due to acid suppression therapy, use of antibiotics, atrophy of gastric mucosa or possibly from poorly preserved histological samples. At the time of the initial visit, there were only limited possibilities to receive acid suppression therapy; according to study protocol two of these 4 subjects had used an antacid within one month before the initial visit but none had used any antibiotics in that time period. One control subject showed atrophy in both antral and corpus mucosa, but interestingly, all the four subjects were suffering from chronic gastritis, which in turn may point to the possibility of false negative finding. *H. pylori* is commonly acquired in childhood (Rowland *et al.* 2006). A finding of an *H. pylori* infection that has been apparently first acquired in adulthood, should be interpreted with caution as has been proposed in the literature (Weck & Brenner 2011). Re-infection with *H. pylori* in adulthood occurs in a minority of subjects after eradication of *H. pylori*; one potential re-infection mechanism is that *H. pylori* spreads from the oral cavity where *H. pylori* have been detected (Rasmussen *et al.* 2010). At the time of initial endoscopy, disinfection of the endoscope was done.
manually, and endoscopic transmission cannot be excluded (Wu et al. 1996). Overall, the suspicion must be that these were false negative findings.

It is not known for sure whether gastric erosions are related to symptoms. Originally in this study, all patients and controls were examined for dyspeptic symptoms or upper abdominal pain. At the initial visit, upper abdominal pain was slightly more often experienced by the patients than the controls. However at the follow-up visit, the prevalence of symptoms was similar (70% in both groups). Furthermore at the follow-up visit, no differences in the pattern of symptoms between the groups or any relationship to concurrent erosions could be seen. Lehmann et al. (2000) examined asymptomatic volunteers and detected an 8% gastric erosion prevalence. These observations indicate that the gastric erosions may be asymptomatic or related with dyspeptic symptoms or pain, but the symptom pattern does not help in the identification of the subject with erosions or erosions with a tendency towards chronicity or recurrence.

No difference in overall mortality was seen between the patients in the erosion group and controls after 16 years of follow-up. No deaths were related to gastric erosions. However, significantly fewer erosion patients had diagnosed malignancies than the controls. In both groups there were different types of malignancies without there being any characteristic pattern. No conclusions about the clinical significance or mechanisms of the observed negative association between erosions and malignancy may be drawn, because of the low number of patients, although one factor may be a protective effect of NSAID use.

In conclusion, this long-term follow-up study found that a significant proportion of gastric erosions are chronic or recurrent. The occurrence of chronic or recurrent gastric erosions is a condition, which is mainly without any major local or systemic consequences as revealed by the clinical history of the subjects. However, nearly 20% of patients with erosions will develop a peptic ulcer, and patients with erosions should be examined for potential causes, such as *H. pylori* infection or use of NSAIDs, and treated accordingly.

### 6.6 Future aspects

One future challenge will be to confirm that an HSV infection is indeed responsible for chronic/recurrent gastric erosions. If samples from the deep nerve ganglia could be taken, culturing HSV or assaying it by PCR or immunological methods might permit identification. These results need to be validated, for example, by examining the occurrence of HSV in subjects known to either have
or not have ulcers as well as individuals without previously any known upper gastric diseases.

From a pathogenetic point of view, it would be beneficial to understand how the presence of *H. simplex* can enhance the formation of erosions. Possible mechanisms might include a modification of mucosal immune activity or acid secretion.

The necessity of treatment and if need, what is optimal treatment of erosions are unresolved issues. In cases where the role of HSV is confirmed, studies of the efficiency of antiviral treatment are warranted.

Erosions are etiologically heterogeneous. New knowledge of etiological factors should be incorporated into the erosion classification. In addition, the endoscopical and pathological criteria for diagnosis and classification should be renewed to include relevant etiological and prognostic aspects. Furthermore, the differential diagnosis of ulcers and erosions should be emphasized. It is probable that some lesions classified as ulcers probably are erosions. New endoscopical methods like high definition endoscopy and endoscopical ultrasound might well provide useful information to enable a more precise differentiation between ulcers and erosions. Simply magnifying endoscope is unlikely to be valuable in distinguishing erosions from ulcers, as in the present study, the criteria for distinguishing erosions from ulcers is based on the known fact that when the lesion is pinched, an erosion can be lifted outwards, but not an ulcer. In addition, it also based on the fact that an erosion does not interrupt the passage of the peristaltic wave.

Non-invasive markers should be developed. Initially they would be used for research purposes, but subsequently they might be able to separate ulcers and erosions correctly without the need for biopsy.

Finally, the clinical value of erosion is that it is benign, and it must be distinguished from ulcers, and also an erosion finding be an indication for eradication of infection in *H. pylori*-positive subjects.
7 Conclusions

1. Gastric erosions are chronic/recurrent in one third of cases after nearly twenty years of follow-up.
2. The association of high titres of HSV antibodies with chronic/recurrent erosions suggests that a significant proportion of chronic/recurrent gastric erosions are related to HSV infection, but not to *H. pylori* infection or to the use of NSAIDs.
3. Focally enhanced inflammation is a characteristic of gastric erosions. Its association with high HSV titres or use of NSAID suggests that these factors could participate in the pathogenesis of gastric antral erosions. Active inflammation in the erosions predicts their chronicity or recurrency, as do high HSV antibody titres. Gastritis in *H. pylori*-positive subjects with gastric erosions shows an evolution towards antral predominance. In contrast, body predominance, including the development of atrophic changes, is rare. Accordingly, patients with erosions share the characteristics of the gastritis encountered in the duodenal ulcer phenotype. These findings emphasize the importance of *H. pylori* and gastric acid in the pathogenesis of chronic/recurrent gastric erosions in *H. pylori*-positive patients.
4. Chronic or recurrent erosions are mostly without serious complications. However, *H. pylori*-positive patients exhibiting erosions do seem to exhibit a significantly elevated risk to develop a peptic ulcer.
References


Morgagni J (1761) De sedibus, et causes morborum per anatomen indagatis.


Original publications

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A LONG-TERM FOLLOW-UP STUDY