THE SØRREISA GASTROINTESTINAL DISORDER STUDY

Dyspepsia, peptic ulcer and endoscopic findings in a population.

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## Abstract

## Acknowledgements

## Preface
- Personal background
- Introduction to scientific work

## 1. Introduction

## 2. Design of the Sørreisa gastrointestinal disorder study

### 2.1. The idea

### 2.2. The process

### 2.3. The discussion

### 2.4. Ethical considerations

### 2.5. The objectives of the study

### 2.6. The final design

#### 2.6.1 The questionnaire survey

#### 2.6.2 The matching procedure

#### 2.6.3 The clinical examination and blood sampling

#### 2.6.4 The endoscopy survey

#### 2.6.5 The histopathological examination

#### 2.6.6 The microbiological examination

#### 2.6.7 The serological examination

#### 2.6.8 The examination of medical records

#### 2.6.9 Definitions

## 3. List of publications

## 4. The main findings

### 4.1. The prevalence of dyspeptic symptoms, non-ulcer dyspepsia and peptic ulcer.
4.2. Associations between dyspepsia, non-ulcer dyspepsia and peptic ulcer and risk factors.

4.3. The endoscopic and histological findings

4.4. Helicobacter pylori

4.5. The clinical examination

5.0 General discussion

5.1. Methodological considerations

5.1.1 The cross sectional design

5.1.2 Reporter bias

5.1.3 Observer bias

5.2. Discussion of some main findings

5.2.1 The occurrence of dyspeptic symptoms and their pattern

5.2.2 Dyspepsia and endoscopic and morphological findings

5.2.3 Helicobacter pylori

6. Epilogue

6.1. Reflections about non-disease

6.2. The importance of Helicobacter pylori

6.3. Personal views

7. References

8. Tables and figure

9. Publications

10. Appendix

   - Questionnaire
ABSTRACT

The Sørreisa Gastrointestinal Disorder Study was conducted in 1987 as a collaborative work between The University of Tromsø, The University Hospital of Tromsø and the Primary Health Care Centre of Sørreisa.

The study was designed to study the prevalences of gastrointestinal symptoms, non-ulcer dyspepsia and of peptic ulcer in a general population. Further to investigate the relation between non-ulcer dyspepsia and peptic ulcer by their distribution in this general population and their associations to lifestyle and psychological factors, and to explore the occurrence of endoscopic, microbiological and histological findings and their associations to dyspeptic symptoms.

The study comprised a survey by a postal questionnaire with 119 questions on abdominal complaints, health, lifestyle, diet and social conditions sent to all inhabitants 20 to 69 years old. A clinical investigation of all dyspeptics and of matched controls, including an upper endoscopy and blood sampling, was done. All medical records in the Primary Health Care Centre were searched for confirmation of a peptic ulcer diagnosis and if the subjects had consulted for dyspeptic problems.

The questionnaire response rate was 88.9% among 2027 men and women. Subjects ever having upper abdominal pain for at
least two weeks and/or heartburn or acid regurgitation almost daily for at least one week's duration were considered having dyspepsia. Of 495 subjects having dyspepsia, 137 were excluded, leaving 362 subjects, of whom 309 together with 310 controls were endoscoped (79.2% of all subjects invited) in a blinded procedure.

Men reported dyspepsia (30.4%) and peptic ulcer (8.7%) more often than women (24.1 and 5.2%, respectively). Peptic ulcer had an overall prevalence of 10.5% in men and 9.5% in women and a higher duodenal/gastric ulcer ratio than reported earlier in northern Norway and the earlier opinion on sex ratio for peptic ulcer is questioned. Asymptomatic subjects had peptic ulcer in 1%. Non-ulcer dyspepsia was frequent in both genders and age groups up to 60 years, with a marked decrease above this age. Non-ulcer dyspepsia was associated with having a family history of peptic ulcer and dyspepsia and the use of tranquillizers. Dyspepsia is common, but seldom associated with peptic ulcer up to the age of 40 years.

Only 10-15% of both dyspeptic and asymptomatic subjects had a histologically normal mucosa. Only peptic ulcer disease, endoscopic duodenitis and histologically confirmed active chronic gastritis were found more often in dyspeptic than in asymptomatic subjects. Helicobacter pylori positive cultures from gastric mucosa were found in 48% of dyspeptic subjects.
and in 36% of asymptomatic subjects. Positive Helicobacter pylori cultures were associated with gastritis and peptic ulcer. Pathological findings in the duodenal and gastric mucosa are frequent and there is with few exceptions, a lack of association with dyspepsia.

The findings challenges gastroenterologists and pathologists to search for new distinctions between disease and non-disease. The epidemiological approaches are mandatorial when new diseases are identified or new technology is introduced as a routine among our armamentaria.
ACKNOWLEDGEMENTS

I am grateful to my superior and friend professor Per G. Burhol who, with all his skills and experience, must have known what he did, what I did not, when he led me into the first steps of scientific work. I am still awaiting his story: "How to recruit research fellows against every odds".

I am constantly aware of my luck and am grateful for the fortunate meeting with people from the Institute of Community Medicine in Tromsø, where I could overcome a somewhat difficult position as an elderly novice, due to a respectful treatment and adequate education. The open doors at the Institute gave me access to several high quality researchers who gave me practical help with many items. I must mention professor Egil Arnesen, professor Olav Helge Førde, The late secretary Gunn Eva Andersen, assistant professor Tormod Brenn and Gunnar Ellingsen.

Primus inter pares was my colleague and friend professor Roar Johnsen, now just primus, but still the indispensable guide, inspirator, teacher and discussion partner through my work with the Sørreisa GID study.
Associate professor Bjørn Straume has been my co-worker and teacher, managing to combine these tasks and still being my friend, comforting me with excellent home-made food, beverages and long-standing conversations.

The nurses Selma Eri Finnseth, Lise Gulbrandsen and Martha Øvermo, were my good helpers and companions in Sørreisa, who, besides doing skilled work, helped to keep a high spirit and to give me lessons on Sørreisa.

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Personal background.

I had been a clinician and gastroenterologist for years and years, and concentrating on patient problems and specific clinical topics, I had forgotten what medicine else could be. I had forgotten to look outside the hospital, and small glimpses of the outer world were soon forgotten in this absorbing environment.

During a short stay at the University Hospital in Tromsø in 1986, I was confronted with a new upcoming idea of a scientific work about non-ulcer dyspepsia. The exciting idea was to find the patients with dyspepsia before deciding to see their doctor and to relate their dyspepsia to environmental and clinical findings. I found it very interesting and accepted to be a co-worker. After some time I found myself working only together with professor Per G. Burhol on these plans and was soon thereafter the leader of a small team. During several meetings with people from the outer world, foremost epidemiologists, I began to realise that many aspects, not inherent in daily clinical work, had to be considered.
Introduction to scientific work (The scientific story).

Non-ulcer dyspepsia was becoming a very popular topic and we followed the development of scientific work in this field. We found the work of Olof Nyrén from the Uppsala county most impressive and this work nourished our idea of going to the very bottom of our source of patients (1). Dr. Nyrén had investigated dyspepsia patients from the Uppsala county during two years and had used population controls in a case control study. He concluded that non-ulcer dyspepsia was not significantly associated with organic diseases and that the condition might be a disease entity with a different pathophysiological mechanisms from duodenal ulcer, and psychological factors might be crucial in the aetiology. From his case-control study he concluded that acid reduction therapy was without beneficial effect in non-ulcer dyspepsia (2). We were curious to relate non-ulcer dyspepsia to other possible pathogenetic factors and especially to see if non-ulcer dyspepsia was related to life-style and social factors.
1. INTRODUCTION

Somebody in your nearest surroundings will have digestive disorders if you do not have these problems yourself. People will try to describe their digestion problems with words or other expressions varying in time and cultural settings and doctors have used much fantasy to interpret them. The aetiology of symptoms is unclear. Symptoms have a great variability and despite attempts to understand digestive symptoms and to classify them on the background of culture and environmental conditions, on pathogenesis or aetiology, these attempts have not been entirely satisfying (3). Authors agree that dyspeptic symptoms are common (4,5) but it is difficult to define exactly what dyspeptic symptoms are (6). Besides, having tried to define special groups of dyspepsia, many authors temporarily used terms, like x-ray negative dyspepsia (7) and pseudo-ulcer syndrome (8) and more actual definitions like non-ulcer dyspepsia and epigastric distress syndrome (1). We have lately made little progress in understanding dyspepsia and relating the symptoms to disease (9) and the natural course of dyspepsia is known only to a modest extent. Scientific interest in dyspepsia has in our near past mainly been concentrated upon the relation to peptic ulcer and other changes in the mucosa seen endoscopically or microscopically
(10,11). The diagnostic methods have been limited and diagnoses have relied upon techniques mostly available in hospitals or specialist centres. General practitioners have selected patients for diagnostic procedures with the idea that type and severity of dyspepsia would predict the important diagnoses (12-14).

Epidemiology.

Epidemiologists will look at the distribution of dyspeptic symptoms in a population to see if it can give an indication of the origin of symptoms, culturally, environmentally or genetically. Modern population based studies on dyspepsia stresses the high prevalence and also a high incidence and that dyspepsia consumes a great amount of health services (15,16).

The Pathogenetic viewpoint.

We have a long tradition of explaining dyspepsia pathogenetically on the basis of historical studies (17). Earlier this tradition was dominated by x-ray studies of motility and structure of the upper gastrointestinal tract. Lately we have got the endoscopic studies emphasising mucosal
pathology. We also had a long period of studies on gastrointestinal hormones and secretion studies, also concentrating on the functional putative pathophysiology of the upper gastrointestinal tract. And again we are moving into studies on motility by ultrasound techniques.

Specific diagnoses:

Gastritis

Dyspeptic symptoms have in modern time in the opinion of doctors been related to peptic ulcer and gastritis (12) but also to functional disorders (6). Gastritis was for a long time used synonymously with dyspepsia (16). The development of fiberoptic endoscopes with biopsy facilities have changed this diagnosis to a pathological anatomic diagnosis. Gastritis prevalences have been obtained in great population studies, showing that gastritis is common, increasing with age, but not associated with dyspeptic symptoms (13). New interest and progress in the understanding was stimulated by the rediscovery of curved bacteria in the stomach mucosa, now Helicobacter pylori (H. pylori) (19). The initial process of inflammation is associated with the occurrence of Helicobacter.
Peptic ulcer

Peptic ulcer occurrence has varied with time and location and has been an enigma for clinicians and scientists. Diagnosis of peptic ulcer has evolved from merely using clinical observation to x-ray investigation and lastly endoscopic visualisation with possibilities for biopsies and histological verification or exclusion of malignancy. During the last 50 years, peptic ulcer has been found more frequently in men than in women in western countries. When subdividing peptic ulcers into gastric and duodenal ulcers this sex difference is found mainly to apply to duodenal ulcers, whereas gastric ulcers have been found about equally frequently in both genders. The scientific work on ulcer aetiology has mainly concentrated upon acid secretion and acid secretory related physiology and during the nineteen-seventies great achievements in ulcer therapy took place (20). The rediscovery of spiral bacteria in the stomach mucosa in 1982 and the research on Helicobacter pylori, has turned research on peptic ulcer aetiology in a new direction and ulcer occurrence may also be better understood (21). There are, however, still some questions to ask. We do not know the natural course of Helicobacter pylori (H. pylori) infection
and we do not know the long term effect of H. pylori eradication.

"Localisation" of dyspepsia

Modern scientific studies and new methods have required subdivision of dyspeptic symptoms aiming at a better understanding of the nature of the symptoms (3). Many researchers have used hospital patients for their studies. This has made it difficult to agree on definitions of dyspepsia and to make comparisons between studies.

Several terms, which were aimed at explaining dyspepsia, have been introduced, like gastritis, duodenitis and gastro-oesophageal reflux without sufficient research to clarify if these terms were meaningful in an explanatory or prognostic context.

In spite of much research, it is still unclear if the findings in the oesophageal, stomach or duodenal mucosa are associated with dyspeptic symptoms. It is also unclear how and to what extent dyspeptic symptoms or the finding of an ulcerous or inflamed mucosa in the upper gastrointestinal tract are associated with life-style, food habits, heredity, infectious disease and other environmental factors.
2. DESIGN OF THE SØRREISA GASTROINTESTINAL DISORDER STUDY.

2.1. The idea

When planning and conducting the study, we had the idea of going to the unselected population to elucidate the basis of selection for diagnostic procedures and treatment. We wanted to register persons having dyspeptic symptoms, to reveal prevalences of non-ulcer dyspepsia, irritable colon and peptic ulcer. We hoped to explore the associations between these entities and living conditions and lifestyle. Furthermore, we wanted to investigate the associations between dyspeptic symptoms and endoscopic findings. We also had the intention to collect a big sample of endoscopic duodenal biopsies and to describe the prevalence of the newly described bacterium Campylobacter (Helicobacter) pylori in dyspeptics.

2.2. The process

The first plans were drawn at the Laboratory of Gastroenterology at the Medical Department of the University Hospital in Tromsø. Several co-workers were involved with professor Per G. Burhol as leader. The group had several meetings where gastroenterologists discussed the items of this
project. We also had a general practitioner in the group Per A. Stakkevold. We had some few meetings with an experienced gastroenterologist and epidemiologist Olav Bonnevie and with an experienced local epidemiologist professor Dag S. Thelle. Later on we formed a smaller group with members from the Laboratory of gastroenterology and from the Department of Pathology at the University Hospital in Tromsø and members from the Institute of Community Medicine at the University of Tromsø. The members in this group were professor of gastroenterology Per G. Burhol, consultant pathologist Leif Bostad, research fellow in general practice Roar Johnsen, associate professor in epidemiology Bjørn Straume, general practitioner Per A. Stakkevold and myself as the leader.

2.3. The discussion

The discussions were mainly concentrated on a few topics: the questions in our questionnaire, the possibility of performing gastroscopy on healthy people, the possibilities of blinding on different levels and feasibility of the procedures performed in a local health centre.

The work with our questionnaire was an exhausting task. Firstly the discussion on characterising dyspepsia. Secondly lengthy discussions on possible risk factors, by dint of
searching in the literature and the use of strong fantasy. The first idea during this work was to evaluate the questionnaire and offer an upper endoscopy to all dyspeptics. Our experienced epidemiologists, however, convinced the group, after some discussions, of the absolute need of having healthy controls.

The third point was a discussion on how to perform an unbiased endoscopy procedure. Our resources of experts for endoscopy were one person, and we did not have the possibility to make video-taping of the endoscopies. This possibility was at hand only for a couple of days to record the routine of the procedure.

We chose a case-control setting to be able to evaluate whether our findings in dyspeptic subjects were directly related to their symptoms. Control subjects would be people without any experience of dyspepsia. We needed for this purpose a well defined population with minimal migration.

The Sørreisa community; why Sørreisa?

As a lucky coincidence we had, as mentioned above, the experienced general practitioner Per A. Stakkevold at the department. He told us about his work in the community of Sørreisa. This community had a stable population and health
service had been well functioning for a long period and seemed suited for our purpose, a population based study on dyspepsia and related diseases. The community had an appropriate size of the population with approximately 3500 inhabitants. The age and sex distribution similar to the distribution of the total Norwegian population. One fourth part of the population lived in a small township, the rest scattered over 361 square kilometres. The inhabitants were occupied in industry (Wood processing, metallurgical work, iron and metal work) (24 %), agriculture, forestry and fishing (4 %), construction work (10 %), trading, restaurant and hotel work (13 %) and in teaching, health service and administration (49 %).

The community had only one community health centre and the health services had been stable without vacancies of medical personal for years.

2.4. Ethical considerations

To expose healthy non-dyspeptic people to an unpleasant and potentially risky investigation was discussed thoroughly. Reported complications of gastroscopy and biopsy from the upper gastrointestinal tract in the hands of skilled endoscopists were very infrequent. From the Tromsø Heart Study and other surveys, we were aware of the general willingness of
people from Northern Norway to participate in scientific studies. We were convinced of the importance of having an open policy on the nature of our study. We also discussed the procedures to follow if any illness was found among our study subjects. We had open access to the local general practice and to the University Hospital in Tromsø. We did not discuss problems of medicalisation. With this background, we decided to apply for approval of the project by the Regional Committee for Medical Research Ethics and I met with the committee to explain our methods and our knowledge about complications. Our study and the different methods and procedures were accepted. All persons participating were insured against any damage related to the endoscopic or blood sampling procedure amounting to maximum one million Norwegian Kroner each.
2.5. The objectives of this study were

I. To study the prevalences of gastrointestinal symptoms, non-ulcer dyspepsia and of peptic ulcer in a general population.

II. To investigate the relation between non-ulcer dyspepsia and peptic ulcer by their distribution in this general population and their associations to lifestyle and psychological factors.

III. To explore the occurrence of endoscopic, microbiological and histological findings and their associations to dyspeptic symptoms.
2.6. The final design

Choice of methods

The study was based on three different elements. Firstly, a survey by a postal questionnaire distributed to all persons above 20 years. Secondly, to perform a clinical investigation of all dyspeptics and of matched controls, including an upper endoscopy and blood sampling. The third element was to investigate all local medical records to confirm peptic ulcer diagnoses, to record whether the subjects had consulted their doctor for dyspeptic problems and whether they had undergone diagnostic procedures.

We chose to conduct a study of adult people. We would start at the age of 20 as we could foresee several problems with the participation of younger people, foremost a low response rate. Later on, we decided to stop at the age of 70 years for the same reasons. We composed a comprehensive questionnaire where the questions partly were constructed for the aims of this study, partly were borrowed from other surveys, foremost the Tromsø Heart Study, where questions had been used and evaluated through several population studies. The questionnaire was tested on several healthy people and
some hospital patients to see if the questions were properly understood and also to collect critical remarks.

We defined a group of dyspeptics on basis of the most accepted criteria and decided to have a low grade of selection on severity of these criteria. The intention was to examine all dyspeptics with exception of those having an established diagnosis which we at that time meant could explain their dyspeptic symptoms. Foremost, we thought of peptic ulcer, gallstones and kidney stones. We wanted to compare the findings in subjects with dyspepsia with findings in subjects without these criteria of dyspepsia.

We wanted to have controls without dyspepsia, partly to open for the possibility to do a case-control study, partly as a basis for a possible cohort study. We chose to match controls regarding 10 -years age-group and gender.

2.6.1. The questionnaire survey.

Demographic data of all inhabitants of Sørreisa 20 years or older on December 31. 1986 were delivered from Kommunedata Nord-Norge. A postal questionnaire was sent to every third person on the list on March 25. 1987. On April 21. the questionnaire was sent to every second person of the remaining persons on the list, and the rest of persons had the
questionnaire sent on Mai 11, 1987. People not responding within 2 weeks got a postal reminder. People not answering after one month got a second postal reminder and a telephone call from one of our nurses shortly thereafter. At this call, we became aware of people not wanting to respond of religious reasons, we also got information of people working on ships or in distant regions making it difficult for them to respond. The nurse (Martha Øvermo) had worked for several years in the community health system as a health visitor and had been active in a Maternal and Child Health Centre. She had a thorough knowledge of people in the community and was highly respected. I assume that her presence, together with the other nurses, gave the project a confidence-inspiring face.

The questionnaire was followed by an introductory letter to the participants explaining the reasons for and the aims of the study. The letter clearly emphasised the scientific character of the study. A total of 119 questions assigned to the following 13 blocks: personal data, complaints of digestion, use of medication, former gastroenterological diseases, other complaints and former diseases, data about first degree family members with dyspeptic complaints and peptic ulcer disease in these members, eating habits, diet, leisure physical activity, use of stimulants like coffee tea, use of tobacco, use of alcohol, use of medicines, occupational
relations and finally recent social conditions and economical conditions during childhood.

All incoming answers were recorded at the Institute of Community Medicine at the University of Tromsø in a registration program which had been developed at the University hospital in Tromsø. All registrations were in a later procedure controlled to be in accordance with the actual questionnaires. The data were later on transmitted in an anonymised form to the SPSS-X statistical program for further evaluation and analysis.

2.6.2. The matching procedure

All of the subjects answering positively to the following two questions: «Have you ever had abdominal pain of at least two weeks duration?» and «If yes, was the pain located to the upper abdomen?» or to the question: «Have you ever had heartburn or acid regurgitation almost daily for at least one week? were defined as having dyspepsia. Potential controls were persons answering «no» to the first and the last question. Persons meeting the inclusion criteria as dyspeptics were matched with controls for sex and 10-years age-group. The controls were found among all the potential controls by a standard data program for randomisation.
2.6.3. Clinical examination and blood sampling.

All subjects were weighed. After this procedure they could lay down and pulse, heart sounds were registrated. Neck and abdomen were palpated and only occasionally other clinical examinations were used. A blood sample was drawn, cooled and centrifuged and the serum stored in a freezer at minus 20 degree C.

2.6.4. The endoscopy survey.

We wanted to do an endoscopy of all dyspeptic subjects and matched controls. After evaluation of the questionnaires at the Institute of Community Medicine, dyspeptics and random age and sex-matched controls were included in a daily schedule and offered an endoscopy by a postal letter. Subjects could alter their appointment by telephone or by a letter. Persons who did not respond got one reminder by telephone. The subjects met after an overnight fasting, although, subjects meeting after noon could have a light breakfast in the morning. Before endoscopy, the subjects were instructed by the nurses not to reveal anything about possible symptoms or history of former disease. They were informed about the
procedure and after endoscopy informed of major findings like peptic ulcer. Before endoscopy they were offered an intravenous injection of diazepam 5mg and Xylocain jelly 2% to swallow.

Endoscopy

A fully equipped endoscopy laboratory was set up in the local health center. We were equipped with new Olympus fiber gastrosopes GIF type Q 20, an Olympus halogen light source type CLE 3 and an Olympus endocamera for pictures. We also had a mobile suction unit and special equipment for lavage and disinfection of the endoscopes and biopsy forceps. For disinfection we used a commercially available glutaraldehyde solution (Korsolin; Norforma, Rud, Norway). After endoscopy, the instruments used were instantly washed with soap water, water and than put into a disinfection solution. After disinfection the instruments were washed with water and thereafter all channels in the endoscopes were pertubed with 70 % alcohol.

The endoscopist was trained from 1975 in endoscopy both in national and foreign university laboratories of gastroenterology (Kommunehospital, Århus, Denmark and Ullevål sykehus, Oslo, Norway) through several courses in endoscopy.
and had performed over 10,000 endoscopies and had trained new endoscopists. The nurses were trained at the University Hospital Laboratory of Gastroenterology in Tromsø. In setting up of the local endoscopy laboratory one senior nurse from this laboratory supervised the installation and the hygienic routines.

2.6.5. The histopathological examination

Biopsy specimens were taken from the distal and proximal duodenum, from the lesser and greater curvatures of the antrum and the corpus of the stomach and also from all lesions. The routine biopsy specimens were placed on a millipore paper on one line in a fixed order, placed in a formalin tube and labelled with reference numbers. The specimens were fixed and prepared according to standard methods in the University laboratory of pathology in Tromsø. Sections of the specimens were stained with haematoxylin and eosin and periodic acid Schiff and Alcian blue and were examined by one pathologist (Leif Rostad). Biopsies from lesions were separately handled in the routine laboratory of pathology. The pathologist had no clinical information on the subjects. The histological findings were both described in the usual routine mode and the findings plotted in a scheme feasible for computer handling.
2.6.6 Microbiological examination

Biopsy specimens from the stomach, one from the lesser and one from the greater curvature in the antrum were placed in 0.5 ml of sterile glucose/saline solution (25 % glucose in 0.9 % saline solution), ground and all material was divided into two equal portions and each portion placed on one blood agar plate and one brain-heart infusion agar containing 5 % horse blood. The media were placed in a Gas Pack jar under microaerophilic conditions (by Gas generating box Campylobacter bioMerrieux) and cultured by 37º C. After 3 days, the jars were transported to a special laboratorium at the University of Tromsø were the specimens were further cultured. The number of colonies was evaluated on a semiquantitative scale: sparsely, medium and rich. After three to ten days, positive cultures were tested for urease, catalase and oxidase activities. Cultures were also Gram stained for microscopic examination. Diagnoses of Helicobacter pylori was based on the positive enzymatic reaction and a typical microscopical appearance after Gram staining. The microbiologist had no clinical information on the subjects.
2.6.7. The serological examination

Serum samples from all endoscoped persons stored at minus 20°C were analyzed in the Microbiological Department of the Oslo City Hospital Ullevål by Ketil Melbye with ELISA technique and a commercial kit «PYLOSET» for Helicobacter pylori antibodies.

2.6.8. The examination of the medical records

Medical records for the total population of the study, both responders and non-responders were examined in the local Community Health Center. All subjects reporting a former peptic ulcer had local medical records. Despite a thorough search for medical records in neighbour municipalities and at the University Hospital in Tromsø, we found no records for 103 subjects, 12 of whom was included in the endoscopy population. We looked for information about consultations for dyspeptic symptoms and evidence of previously diagnosed peptic ulcers by barium studies or endoscopy. We also registered all records of patients seeing their doctor for dyspeptic symptoms.
2.6.9. Definitions

Dyspepsia: all persons meeting the criteria of ever having had pain in the upper part of the abdomen for at least two week's duration or heartburn or acid regurgitation almost daily during at least one week.

Non-ulcer dyspepsia: All persons from the endoscopic study having dyspepsia without a peptic ulcer, deformity of the duodenal bulb or endoscopic duodenitis of the duodenal bulb.

Peptic ulcer: All persons with a verified peptic ulcer diagnosed with x-ray, endoscopy or both. By the endoscopy study peptic ulcer was defined as mucosal defects with the typical endoscopic visible features of a peptic ulcer with a crater more than 5 mm i diameter. All peptic ulcers were in addition biopsied to confirm the ulcer histologically.

Gastro-oesophageal reflux-like (reflux-like) dyspepsia, Ulcer-like dyspepsia and dysmotility-like dyspepsia as defined by Colin-Jones et al in 1988 (3).

Prevalence: For the cardinal symptoms defining dyspepsia, we have used a life-time prevalence in asking people whether they
any time had the symptoms in question. Other prevalences are point prevalences as for endoscopically diagnosed peptic ulcers or other endoscopic findings. Peptic ulcer prevalence was calculated from all former and actual peptic ulcers in an overall prevalence.
3. LIST OF PUBLICATIONS


II. Bernersen B, Johnsen R, Straume B. Non-ulcer dyspepsia and peptic ulcer—Their distribution in a population and their association to risk factors. Accepted for publication in Gut 1995.


4. THE MAIN FINDINGS

4.1. The prevalence of dyspeptic symptoms, non-ulcer dyspepsia and peptic ulcer.

Dyspepsia, according to the definition on page 22, was reported by 30.4% of the men and 24.1% of women. Frequency of dyspepsia increased slightly with age in men, unlike in women where dyspepsia was evenly distributed over all age groups. Stratified for age there were no significant differences in the occurrence of dyspepsia between the genders.

Non-ulcer dyspepsia was estimated to have a prevalence of 12.4% in men and 13.5% in women. The prevalence of non-ulcer dyspepsia was the same in both genders and seemed constant up to the age of 60. Above this age there was a marked decrease in the occurrence (paper 11).

The prevalence of peptic ulcer was estimated on basis of reports from the questionnaire verified in medical records, endoscopy of all dyspeptics and controls by a calculation procedure accounted for in paper 1. One crucial point in the estimation of peptic ulcer is the registration of ulcer scars (foremost deformed duodenal bulbs). The prevalence of reported peptic ulcers was 6.2% in men and 2.7% in women.
The point prevalence of peptic ulcer in the endoscopic study was lower in men (3.6 %) than in women (4.3 %). And the prevalences of deformed duodenal bulbs were also lower in men than in women, 5.9 % and 6.5 %, respectively. Estimated overall prevalences when deformed duodenal bulbs were calculated as former ulcers, were 10.5 % in men and 9.5 % in women, a statistically non-significant difference. At the endoscopy study we found a point prevalence of peptic ulcer in non-dyspeptics of 1%, higher in women than in men (paper I). Peptic ulcer was rare among people under the age of 40 years in men and under 50 years in women. The mean age of subjects with peptic ulcers in the endoscopic study was 45.8 years for men and 45.6 years for women (paper II).

4.2. Associations between dyspepsia, non-ulcer dyspepsia and peptic ulcer and risk factors.

Comparing the associations of reported dyspepsia and non-ulcer dyspepsia with several demographic, life-style and social conditions we found about the same pattern of associations in both. The analysis of the association of dyspepsia to risk factors showed significant associations with sex, a family history of dyspepsia, peptic ulcer occurrence in
the family, smoking, previous smoking, frequent recurrence of herpes labialis and frequent health complaints. In the analysis of non-ulcer dyspepsia the associations were similar, but we here also found associations to the use of tranquillizers and to the feeling of lack of time. Reported dyspepsia was associated to smoking and previous smoking, non-ulcer dyspepsia was not.

The association of peptic ulcer with demographic, lifestyle and social conditions showed a pattern different from that of non-ulcer dyspepsia, firstly to age and gender, but also to smoking, a family history of peptic ulcer and feeling of stress, but also unexpectedly to having been breastfed as a baby. We also found significant associations with frequent recurrences of herpes labialis and poor living conditions. In the light of the last years of Helicobacter pylori research we found it very interesting that both reporting frequent herpes labialis recurrences and poor living conditions during childhood were risk factors for having Helicobacter pylori infection. Study of risk factors showed that both dyspeptics and non-dyspeptics had altered their habits. Teadrinkers controlled for earlier coffee drinking showed that 38 % of dyspeptics and 21 % of non-dyspeptics had stopped coffee drinking (paper II).
4.3. The endoscopic and histological findings

When all criteria for pathological findings, according to the applied definition used, were pooled together, only 10% of both subjects with and without dyspepsia had a normal gastric and duodenal mucosa. Out of five endoscopic and four histological diagnoses, only peptic ulcer, endoscopic duodenitis and active chronic gastritis were diagnosed significantly more often in subjects with dyspepsia compared to non-dyspeptics. Of histological diagnoses, only active chronic gastritis was more frequent in dyspeptics than in controls. A substantial amount of 50% of controls had chronic atrophic gastritis, and 20% of peptic ulcer was found among controls (paper III).

Erosive prepyloric changes (EPC) were described by Nesland and Berstad 1985 (16) as deviations from the normal mucosa, with standing mucosal folds, sometimes with red spots and streaks and sometimes in addition erosions, divided into 3 degrees. In our study we found EPC in 38.5% of dyspeptics and 35.1% of non-dyspeptics, in both groups more frequent in men than in women. Occurrence of Helicobacter pylori was not associated with occurrence of EPC. Endoscopic duodenitis was found more frequently in subjects of the two highest gradings of EPC, and the highest grading was associated with chronic
gastritis. EPC was associated with smoking and in women, in addition, with use of alcoholic beverages (paper IV).

4.4. Helicobacter pylori

Helicobacter positive cultures were found more often in subjects with dyspepsia (48%) than in subjects without dyspepsia 36%. Positive culture in both subjects with and without dyspepsia was strongly associated with histological gastritis and peptic ulcer. Only 3% of subjects with a histologically non-inflamed gastric mucosa had this infection (paper V).

Further studies on this material as yet unpublished, shows that H. pylori positive cultures, when semiquantitatively graded, are for the highest grade found significantly more often in dyspeptics than in non-dyspeptics. Of dyspeptics 96, and of non-dyspeptics 59 subjects had this highest grade of H. pylori growth (Table 1). We found significant differences in frequency of oesophagitis between dyspeptics and non-dyspeptics 11.5% and 3.4%, respectively, and we also found a in frequency of endoscopic duodenitis with 24.0% and 6.8%, respectively. When histological diagnoses were analysed for this group of H. pylori positive subjects, there were no differences between dyspeptics and non-dyspeptics (Table 2).
Unfortunately, we had no help from serological studies in evaluating the \textit{H. pylori} infection because of poor specificity. We do not know the cause of this result, but at least one reason may be cross reactions to campylobacter jejuni antibodies.

4.5. The clinical examination

We searched for tender points in the abdomen by palpation and let the subjects eventually point them out, but we found no association between tenderness in the upper abdomen and peptic ulcer or duodenitis.

By the clinical examination of the abdomen we found one middle aged woman and five middle-aged men having an enlarged liver. Two women had situs inversus, one at the age of 68 years who knew of her situs inversus and one 22 year old woman who remembered her mother mentioning something of her heart being located on the right side. A 66 year old man had an aortic aneurism which was confirmed by aortography at the University Hospital in Tromsø. Due to the lack of surgical capacity, he was discharged, and a month later successfully treated in an emergency operation after rupture of his aneurism. Another woman had a greenish corneal ring, best
fitting the description of a Kaiser-Fleischer ring, but without corresponding clinical or biochemical findings.
5. GENERAL DISCUSSION

5.1 Methodological considerations

This population based study of dyspepsia, peptic ulcer and endoscopic findings has several advantages: a substantial response rate of 88.9% on the questionnaire survey and an attendance rate of 79% in the endoscopy study, a diagnostic endoscopy performed in both dyspeptics and non-dyspeptics, blinding of all diagnostic procedures, and unique possibilities for search in medical records for the results of previous diagnostic examinations. Despite the high response rates there are still some non-responders, and any chosen definition of dyspepsia for endoscopy would represent a potential for selection bias. We chose to reveal the whole "ice-berg" of symptoms and clinical findings without selection on severity of symptoms. We tried, however, to keep the definition of dyspepsia within the frames of international accepted definitions. The main methodological weaknesses of this study are the lack of dimensions on intensity of symptoms, whether the reported dyspepsia represented current complaints, and the cross sectional design. Other problems are the selection bias for endoscopy by exclusion of subjects with self-reported peptic ulcers and the lack of assessments of
inter-and intra-observer variation. The first two problems will be discussed in the chapter: Dyspepsia and endoscopic and morphological findings (5.2.2. on page 50).

Non-response is a modest problem for the conclusions of this study. Among the non-responders we had an overrepresentation of the youngest age group and an underrepresentation of the age group 50-69 years both in men and women. By examination of the local medical records, we found significantly fewer peptic ulcers in this group than among responders. From these data it may be assumed that the non-responders had fewer problems related to the gastrointestinal tract and thus were less motivated for participation in this survey. Especially, among young people, there were some persons working outside the community where they may have had their health service, but, unfortunately, we do not have information about this group. There was also a small group of religiously active people (Maran Ata) not participating of religious causes. The local church authority had listed approximately 20 people of this religious congregation. Several non-responders are sailors or people temporarily working outside the hometown. Presumably this latter group consists of people disposed to dyspeptic symptoms. We have, however, no information about complaints and diseases in this group.
Subjects who reported peptic ulcer disease, were in our design excluded from the endoscopy study. We supposed that these subjects had had some diagnostic procedures with peptic ulcer as the explanation of their symptoms. As our capacity for endoscopy was restricted, we considered a new endoscopy of these subjects of less importance compared to the possibility to endoscope undiagnosed subjects with dyspepsia. The exclusion of this group of dyspeptics represent a potential selection bias which must be taken into consideration when comparing findings in dyspeptics and non-dyspeptics. This group of dyspeptics may have had a higher score of pathological endoscopic and histological findings. However, would also their potential controls have had a substantial amount of pathological findings, peptic ulcer included.

5.1.1. The cross sectional design

The cross-sectional nature of this study makes it impossible to study causality. The study has, however, been used to elucidate and question some conventional conceptions. In our cross-sectional perspective of the population of Sørreisa, we have used gross characteristics as sex and age. Use of more sophisticated parameters may, however, be
difficult. Even generally accepted risk factors could be disturbed in a cross-sectional design due to change of habits. An example is our findings of coffee and tea-drinking in relation to dyspepsia. Special groups of a population may be more aware of possible risk behaviour, which is then readily altered when symptoms or suspicion of disease comes up.

5.1.2. Reporter bias.

We had no possibility to estimate the magnitude of reporter bias except for the reporting of peptic ulcer. By searching all local medical records, we were unable to confirm 15.3% of men's reports of peptic ulcer and 20.3% of the corresponding reports in women. For false negative reports the numbers were 1.3% and 0.2% in men and women, respectively. It must be pointed out that all persons reporting an ulcer had been admitted to a diagnostic procedure with x-ray or endoscopy or both, so that their reports of having peptic ulcer may merely be a matter of a communication problem, or perhaps an example of over-interpretation of findings.

Medical records for 103 persons were not at hand, which we regarded negligible in this context. None of those reporting peptic ulcers were among those with missing records.
5.1.3. Observer bias

The main objections to the presented results are the possibility of observer bias. The endoscopic study was performed with the endoscopist blinded for whether he examined a subject with or without dyspepsia. The blinding procedure was performed successfully with the cooperation and understanding of every person endoscoped. All specimens, whether sent to histopathology or to microbiology, were identified with numbers. These were all procedures designed to avoid observer bias. However, all the interpreters were aware of the design of the study and that the examined specimen was from a study participant. The effect of this knowledge on the diagnostic results is unknown. No procedure addressing on inter-intra-observer variation was planned, but would not have given relevant information about such potential bias, because all participants would have been informed of the scientific nature of this study. However, unintentionally, we have got the opportunity to compare different examination procedure of Helicobacter pylori (Table 1 and 3). Table three indicates some disagreement in the morphological identification of H. pylori between the two pathologists. The interpretations showed both, a significant but opposite difference between dyspeptics and non-dyspeptics. Not
surprisingly, most of the disagreement was connected to the interpretations of the culture negative specimens and those with a corresponding low graded growth (table 3). The proportional agreement for diagnosis of H. pylori from specimens with growth graded II or III was very good. Using cultures as a reference standard, the main problem of morphological diagnosis of H. pylori seems to be the amount of false positive H. pylori diagnoses and a corresponding low specificity. It is again an important reminder for including inter-intra-observer studies when clinical observation is used as basis for diagnosis. Fortunately, all observations and diagnosing in this study were performed blindly, and should therefore not have interfered on the distribution of findings between dyspeptics and non-dyspeptics.

5.2. Discussion of some main findings.

5.2.1 The occurrence of dyspeptic symptoms and their pattern in the general population.

The main dyspeptic symptoms usually ascribed to the upper gastrointestinal tract are epigastric pain (in its classical form relieved by drinking milk or by eating), sometimes occurring during the night, and heartburn, aggravated by
stooping or by laying in flat posture. Different from these symptoms are symptoms usually referred to as low abdominal pain, diffuse abdominal pain usually combined with bloating, early satiety, nausea and alternating constipation and frequent loose stools. The key symptoms were in this study epigastric pain and heartburn. It is therefore interesting to notice that concomitant symptoms to pain, were reported at the same level in association with abdominal pain and diffuse pain, as to epigastric pain and heartburn (Table 5). So the pattern of reported symptoms did not indicate a special «upper gastro-intestinal tract» pattern. The predictive properties of epigastric pain and heartburn are, however, not better regarding organic diseases than are combination of symptoms with abdominal pain of any location (14,22).

Most people with dyspepsia do not have severe organic diseases and a great proportion of people with gastritis or H.pylori infection do not have symptoms. There have been attempts to group specific symptom complexes, like that of the working party for management of dyspepsia around Colin-Jones (3). Patients without a peptic ulcer or other major pathological findings (endoscopy negative dyspepsia) are grouped into different syndromes according to cardinal
symptoms, like: reflux-like dyspepsia, dysmotility-like dyspepsia, ulcer-like dyspepsia.

Reasons for grouping symptoms into syndromes might be:

1) The groups reflect patterns found in the patient populations.

2) The syndromes represent entities carrying prognostic knowledge.

3) The syndromes could reflect knowledge of aetiology and/or pathogenesis.

For the definitions used by the group around Colin-Jones, the last two assumptions are in my opinion not fulfilled, but will not be further discussed in this context. Regarding patterns of dyspeptic symptoms found in a general population, several authors have questioned the classification of non-organic dyspepsia; Talley among others could not recognise the defined entities in the population of Olmsted County, Minnesota. He also pointed out that patients having symptoms consistent with one group, could be classified in more than one group (9). These objections against an exclusive classification of dyspeptics in one group is supported by the Sørreisa data (table 6). As Talley has shown, there are difficulties in recognising the pattern of dyspeptic syndromes. Among the persons with reported symptoms in accordance with any of the
syndromes, many persons had symptoms which could be placed in several syndromes (Table 6). Lastly the number of persons not «fitting in» in any of the syndromes amounts to 70 % (Figure 1) of the syndromes.

The dyspeptic symptoms overlap and a substantial amount of persons could be allocated to several groups, or the patterns of symptoms did not fit to any group of syndromes.

One objection to the findings is the lack of relevance. The people are not patients, and the pattern among patients would be different. Both patients and the doctors use their preconceived (often anecdotal) knowledge, and therefore their symptom patterns may represent a selection bias, a self reinforced circle arguing. On the other hand we had the possibility to do subanalysis on people visiting the primary physician the last year, those referred to hospital due to abdominal pain and those without contacts with the formalised health care system. There are no differences between the three groups regarding reported patterns of symptoms.

So far, it seems important to identify persons with organic diseases as H. pylori related disease and serious reflux disease which could be treated successfully. Of course malignancy should be recognised, but the rest of the persons with dyspeptic complaints should be reassured and guided regarding lifestyle, diet habits and coping strategies.
5.2.2. Dyspepsia and endoscopic and morphological findings.

The association between different types of gastritis and symptoms has been questioned by several authors (18,23). But the belief in duodenitis as a clinical entity has been strong, and especially morphological duodenitis grade II and III have been recognised as a disease (24,25). Erosive prepyloric changes (EPC) have been claimed as a new disease entity, especially in Scandinavia (26). There have been several critical voices against also this clinical entity.

Except from endoscopic duodenitis and peptic ulcer disease, the endoscopic study in Sørreisa do not support any theories of these entities being diseases associated with dyspeptic symptoms. There are, however, several objections against the findings, all based on the applied definition of dyspepsia. Our definition did not take into account neither the intensity nor the duration of dyspeptic symptoms. The reported symptoms also do not need to be current symptoms.

Unfortunately, we do not have information about the intensity of the symptoms, but indirectly we have some information about the seriousness or grading, as judged by the patients. An indication on the seriousness of the symptoms are the reports on consulting the local health care service due to epigastric pain (table 6). Subanalysis of the number of
persons who had been in contact with the local health care the last year due to epigastric pain, showed the same findings regarding association between symptoms and endoscopic findings as in paper III-Table II. Minor symptoms do not seem to be an acceptable explanation of our findings.

We also have met criticism of the use of dyspeptic symptoms not being current symptoms. When analysing endoscopic and morphological findings in relation to defined dyspepsia and to epigastric pain the last two weeks, there are no significant differences from the results presented in paper III (Table 7).

In conclusion, we may claim that it is unlikely that our findings can be explained by selection of subjects without current symptoms, transitory symptoms or minor symptoms which usually are not sufficiently alarming to release a consultation of the physician. Our findings should inspire gastroenterologists to control our findings for the purpose of avoiding further unnecessary non-disease labels given the explanatory function of dyspeptic symptoms.
5.2.3. Helicobacter pylori

The spiral bacteria which could be seen in the stomach mucosa were for a long time left out of consideration as a pathogen, probably because it was difficult to culture and study the bacteria. Now the diagnosis of H. pylori infections seems to be a matter of routine. Authors agree that testing or growing tissue from the stomach mucosa is an excellent method of detection with a high specificity. Routine staining and special staining of biopsies are good methods, but may be less sensitive and less specific. Serologic testing is today a simple and very sensitive method, although antibodies may remain for years after clearance of the bacteria. The urea breath test is now a very sensitive method of detection with a high specificity, but a grading of the bacterial growth or activity will be difficult (27).

In the Sørkreia survey we chose to culture biopsies for a specific diagnosis as a reference standard. Culture is, however, a difficult method and we know that bacterial growth can be hampered by transport, antibacterial agents or inadequate culture methods. Our results showed discrepancies between culture and morphological diagnosis. An exact diagnosis morphologically seems difficult with reference to the differences in diagnosis between pathologists. Serology
was with the methods used in our material not sufficiently specific (table 1). This may be a problem in populations with a high frequency of campylobacter jejuni infection due to cross-reactions.

Our investigation shows that there is an association between the high grade of growth of H. pylori in our cultures and the morphologic diagnosis (Table 2).

We found only a weak association between H. pylori infection and dyspepsia in our total material. The finding of a significant difference between dyspeptics and non-dyspeptics for only the highest grade of H. pylori growth from antral biopsies, may be a reason to reconsider our interpretation. There is in the highest grade of H. pylori growth a significant difference between dyspeptics and non-dyspeptics (table 1). Still one fifth of the non-dyspeptics had an infection with H. pylori where the growth was classified as grade III. For the lesser grades of growth there was no association to the dyspeptic symptoms. One may considerate whether activity or intensity of the infection could have some importance for the symptoms. It is also interesting that endoscopic duodenitis and oesophagitis are found significantly more often in dyspeptic subjects with H. pylori infection than in subjects without dyspepsia. If H. pylori is of etiologic or pathogenetic importance for peptic ulcer, then it is possible
that endoscopic visible duodenitis is a stage in the
development of duodenal ulcer.

Our study has inspired us to question the up to date
belief of H. pylori as the causal factor of peptic ulcer. We
know from research over the past century that peptic ulcer
disease must be multifactorial and that pepsin and acid
secretion are crucial in the pathogenesis of the ulcer. At
least one must admit that H. pylori infection and gastritis
per se is a very common state, but only a small part of
subjects with this infection will have a peptic ulcer. There
must be another factor or several factors which activate the
infection. In our material, we found different stages of
H.pylori status. Firstly one stage with only morphological
detection of the bacteria, one second stage with both positive
culture, positive morphology and a high level of
seropositivity and thirdly a stage only with positive
serology. It may be possible that H. pylori infection which
around the world is very common, at one stage or in some
persons causes an immunological reaction which can develop
into peptic ulcer or an atrophic gastritis.
6. EPILOGUE

6.1. Reflections about non-disease.

When looking back at the results of this study, one of the stunning observations was the great amount of ascribed pathology in apparently healthy people. At least one must admit that these persons did not report dyspeptic symptoms. Should these people of ethical reasons be informed of their pathology, and should these findings have consequences for counselling or therapy? What about patients seeking their doctor for dyspeptic symptoms? Does the finding of gastritis endoscopically or histologically explain their symptoms, and would any treatment directed against this inflammation be appropriate? Which lesson could be taught from the example of Erosive prepyloric changes (EPC).

In our material, there were no common gastrointestinal symptoms associated with EPC. It is tempting to call upon the thoughts of Meador some 30 years after his excellent paper on the art and science of non-disease (28). The temptation is to classify the histological diagnosis of duodenitis and gastritis as well to his class of Overinterpretations-of-physical-findings-syndrome or perhaps more specifically into the Overinterpretation-of-endoscopic-findings-syndrome. That
is the reason why our controls not should be named healthy controls, but more preferably non-dyspeptics. The described phenomena are not false positive findings, but irrelevant explanations of dyspeptic symptoms. It is the physicians task to take serious patients concerns due to symptoms. Labelling of symptoms, like gastritis, is in fact to create a non-disease, which in turn causes more distress and endless search for cures, supporting unserious participants of the authorised and non-authorised health market. This tendency can be observed in several fields where new diagnostic technology is applied, and new findings uncritically are accepted as a reason for complaints or dysfunction (29).

Before the medical society accepts any use of new therapeutic regimens, it legitimately asks for properly designed trials. Likewise, should the same society ask for specifically designed studies in advance before the interpretation of new technological findings are applied.

6.2. The importance of Helicobacter pylori

Helicobacter pylori (H. pylori) has in the opinion of very many researchers and clinicians got the status of the etiologic agent for gastritis, peptic ulcer and an important
role in the pathogenesis of gastric carcinoma. Most clinicians recommend to treat the infection in peptic ulcer patients. The effect will be a lower recurrence rate, especially for duodenal ulcer. The observations on recurrence of peptic ulcer published, have mostly covered one year. We do not know what happens to the peptic ulcer patients on a long term after H. pylori eradication. Eradication of H. pylori as a treatment of non-ulcer dyspepsia has given uncertain results, but may give symptom relief in subgroups of non-ulcer dyspepsia (30). The eradication of H. pylori will require the use of one or more antibiotics and maybe potentially toxic agents like bismuth. We also do not know the natural course of H. pylori infection and we do not know to what extent this infection in asymptomatic individuals will cause future clinical disease, but no experts have until this time recommended a prophylactic treatment of the infection, nor programmes to reveal such infections.

On the basis of our work, we would recommend to follow up H. pylori positive individuals both with and without symptoms for a long period to see to which extent asymptomatic individuals are converted into symptomatic ones and vice versa. It would also be interesting to see which individuals need further diagnostic procedures, namely to discover peptic ulcer disease.
6.3. Personal view

The Sørreisa Gastrointestinal disorder study has made it obvious to me that clinicians, every day presented to patients or persons suffering from symptoms, need to be aware of from which pond these symptoms are drawn. Which diseases would these symptoms match, and if these symptoms are an expression of disease? Introduced to fancy and sophisticated tools aimed at detecting disease, we have to be cautious not to give the conditions found the disease-label and in the next moment give our findings the authorisation of an explanation of the symptoms of the patient. Surely is this an old knowledge for clinicians, but examples from my own clinical field show that we have to be very conscious, not to fall into this pitfall.

This study was planned with certain ideas in mind originated in clinicians. We wanted to see which dyspeptic symptoms we could find in an unselected population and which associations they had to disease. We chose to set the focus on dyspepsia compared to the condition of having no dyspepsia. This design of our study has given answers in relation to dyspepsia, but we might as well have done an endoscopy of a random sample of the population. That would have given us the possibility of a wider perspective. Those thoughts are,
however, a belated wisdom and without this study at that particular time, we might not even today have been the owners of that wisdom.

It would be very interesting to see the Sørreisa-population once more. It would be very interesting to see, after a suitable time, what has happened with the dyspeptic persons without disease in 1987. How have dyspeptic symptoms developed? Have some of them got a peptic ulcer disease and who got this disease? Was getting peptic ulcer disease related to any of the factors recorded in 1987? Has Helicobacter pylori been of significance? What has happened to the persons with a peptic ulcer before 1987? Have they suffered from complications? We would also ask those groups of their use of health services and use of medication. How was the development in the healthy controls? Did any of them develop symptoms or disease, and, was in that case disease or symptoms related to factors recorded in 1987, especially to Helicobacter pylori infection?
7. REFERENCES


8. TABLES AND FIGURE
Table 1: The frequencies (%) of Helicobacter pylori identified by different methods in dyspeptics and non-dyspeptics. Sørreisa 1987/88.

<table>
<thead>
<tr>
<th>Identification methods</th>
<th>Dyspeptics (N=309)</th>
<th>Non-dyspeptics (N=310)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Cultures of biopisies:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- growth graded I</td>
<td>21</td>
<td>6.8</td>
</tr>
<tr>
<td>- growth graded II</td>
<td>30</td>
<td>9.7</td>
</tr>
<tr>
<td>- growth graded III</td>
<td>96</td>
<td>31.1</td>
</tr>
<tr>
<td>- total</td>
<td>147</td>
<td>47.6</td>
</tr>
<tr>
<td>Morphology:</td>
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<td></td>
</tr>
<tr>
<td>- pathologist I</td>
<td>194</td>
<td>62.8</td>
</tr>
<tr>
<td>- pathologist II</td>
<td>164</td>
<td>53.1</td>
</tr>
<tr>
<td>Serology:</td>
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<td></td>
</tr>
<tr>
<td>- Pyloset</td>
<td>180</td>
<td>58.3</td>
</tr>
<tr>
<td>- IgG7#</td>
<td>234</td>
<td>75.7</td>
</tr>
<tr>
<td>- IgG8#</td>
<td>215</td>
<td>69.6</td>
</tr>
<tr>
<td>- IgG9#</td>
<td>179</td>
<td>57.9</td>
</tr>
</tbody>
</table>

*The figure indicates the titer where the threshold for positive test was set.
*p<.01
Table 2: The frequencies of some endoscopic and histological findings among the endoscoped persons with growth of grade III of Helicobacter pylori. Sørreisa 1987/88.

<table>
<thead>
<tr>
<th>Endoscopic diagnoses:</th>
<th>Dyspeptics (N=96)</th>
<th>Non-dyspeptics (N=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Cesophagitis</td>
<td>11</td>
<td>11.5</td>
<td>2</td>
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<tr>
<td>Superficial gastritis</td>
<td>22</td>
<td>22.9</td>
<td>9</td>
</tr>
<tr>
<td>Atrophic gastritis</td>
<td>7</td>
<td>7.3</td>
<td>1</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>6</td>
<td>6.3</td>
<td>2</td>
</tr>
<tr>
<td>Duodentitis</td>
<td>23</td>
<td>24.0</td>
<td>4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histological diagnoses:</th>
<th>Chr. atrophic gastritis</th>
<th>Active chr. gastritis</th>
<th>Duodenitis</th>
<th>Metaplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>87</td>
<td>33</td>
<td>65</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>90.6</td>
<td>36.5</td>
<td>67.7</td>
<td>32.3</td>
</tr>
</tbody>
</table>
Table 3: Agreement between two pathologists of morphological Helicobacter pylori diagnosis, expressed as proportional agreement according to graded growth of Helicobacter pylori. Sørreisa 1987/88

<table>
<thead>
<tr>
<th>Cultured antrum biopsies for H. pylori</th>
<th>Proportional agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative culture</td>
<td>.77</td>
</tr>
<tr>
<td>growth graded I</td>
<td>.71</td>
</tr>
<tr>
<td>growth graded II</td>
<td>.84</td>
</tr>
<tr>
<td>growth graded III</td>
<td>.89</td>
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</table>
Table 4: The distribution (%) of reported abdominal complaints by nature and location (N=436) among men and women aged 20-69 years. Sørreisa 1987.

<table>
<thead>
<tr>
<th>Duration of daily pain</th>
<th>Epigastric pain (N=215)*</th>
<th>Low abdominal pain (N=91)*</th>
<th>Diffuse abdominal pain (N=115)*</th>
</tr>
</thead>
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<tr>
<td>&gt;2 months</td>
<td>27.4</td>
<td>33.3</td>
<td>46.4</td>
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<tr>
<td>Pain during the night</td>
<td>36.2</td>
<td>27.1</td>
<td>45.9</td>
</tr>
<tr>
<td>Heartburn or acid regurgitation</td>
<td>50.2</td>
<td>24.2</td>
<td>46.1</td>
</tr>
<tr>
<td>Frequent nausea</td>
<td>16.7</td>
<td>18.7</td>
<td>23.5</td>
</tr>
<tr>
<td>Early satiety</td>
<td>17.1</td>
<td>4.4</td>
<td>20.0</td>
</tr>
<tr>
<td>Meteorism</td>
<td>70.7</td>
<td>67.0</td>
<td>80.9</td>
</tr>
<tr>
<td>Relief of symptoms by defecation</td>
<td>83.6</td>
<td>80.3</td>
<td>83.9</td>
</tr>
<tr>
<td>Obstructed</td>
<td>20.0</td>
<td>20.9</td>
<td>23.5</td>
</tr>
<tr>
<td>Reporting two or more extra-abdominal complaints**</td>
<td>23.3</td>
<td>31.0</td>
<td>39.1</td>
</tr>
</tbody>
</table>

* The denominator varies due to missing answers.
** Based on reports of frequent suffering from headache, dizziness, palpitations, sleep disturbances, joint and muscle pain.
Table 5: Frequency (%) of different categories of dyspepsia by combinations of the same main categories in subjects aged 20 to 69 years. Sørreisa 1987.

<table>
<thead>
<tr>
<th>Category of dyspepsia</th>
<th>Ulcer-like (N=39)</th>
<th>Reflux-like (N=120)</th>
<th>Dysmotility-like (N=219)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combinations n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reflux-like and ulcer-like (31)</td>
<td>79.5</td>
<td>25.8</td>
<td></td>
</tr>
<tr>
<td>Ulcer-like and Dysmotility-like (23)</td>
<td>59.0</td>
<td>-</td>
<td>10.5</td>
</tr>
<tr>
<td>Reflux-like and Dysmotility-like (54)</td>
<td>-</td>
<td>45.0</td>
<td>24.7</td>
</tr>
<tr>
<td>All three categories (20)</td>
<td>51.3</td>
<td>16.7</td>
<td>9.1</td>
</tr>
</tbody>
</table>
Table 6: The frequency (%) of use of health care and use of medication by location of reported pain (N=436) among men and women aged 20-69 years. Sorreisa 1987.

<table>
<thead>
<tr>
<th>Localisation of pain</th>
<th>Epigastric (N=215)*</th>
<th>Low abdominal (N=91)*</th>
<th>Diffuse abdominal (N=115)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of daily pain</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;2 months</td>
<td>27.4</td>
<td>33.3</td>
<td>46.4</td>
</tr>
<tr>
<td>Visiting the local physician the last year</td>
<td>82.9</td>
<td>85.2</td>
<td>84.1</td>
</tr>
<tr>
<td>Referred to specialist due to pain the last year</td>
<td>54.5</td>
<td>51.7</td>
<td>56.5</td>
</tr>
<tr>
<td>Medical certificate/sick leave</td>
<td>21.8</td>
<td>25.3</td>
<td>32.7</td>
</tr>
<tr>
<td>Used antacids</td>
<td>75.4</td>
<td>43.2</td>
<td>66.1</td>
</tr>
<tr>
<td>Used H-2 blockers</td>
<td>40.6</td>
<td>14.8</td>
<td>41.5</td>
</tr>
</tbody>
</table>

* The denominator varies due to missing answers.
Table 7: Prevalences (%) of endoscopic and histological findings in dyspeptics by current dyspepsia and by previous dyspepsia. Sorreisa 1987. (From Roar Johnsen: Population studies on dyspepsia and peptic ulcer disease. Tromsø 1992)

<table>
<thead>
<tr>
<th></th>
<th>Epigastric pain last two weeks (N=84)</th>
<th>Previous dyspeptic symptoms only (N=225)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endoscopic findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagitis (grade I or II)</td>
<td>13.1</td>
<td>11.2</td>
<td>.63</td>
</tr>
<tr>
<td>Superficial gastritis</td>
<td>22.6</td>
<td>19.2</td>
<td>.61</td>
</tr>
<tr>
<td>Duodenogastric reflux</td>
<td>30.2</td>
<td>16.1</td>
<td>.49</td>
</tr>
<tr>
<td>Peptic ulcer disease</td>
<td>10.7</td>
<td>8.0</td>
<td>.46</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>17.9</td>
<td>23.2</td>
<td>.31</td>
</tr>
<tr>
<td>Normal endoscopy</td>
<td>54.8</td>
<td>52.7</td>
<td>.74</td>
</tr>
<tr>
<td>Histological findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic superficial gastritis</td>
<td>24.5</td>
<td>46.4</td>
<td>.06</td>
</tr>
<tr>
<td>Chronic atrophic gastritis</td>
<td>54.8</td>
<td>63.8</td>
<td>.15</td>
</tr>
<tr>
<td>Active chronic gastritis</td>
<td>25.0</td>
<td>25.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>73.2</td>
<td>58.5</td>
<td>.01</td>
</tr>
<tr>
<td>Duodenitis grade II</td>
<td>32.3</td>
<td>35.1</td>
<td>.70</td>
</tr>
<tr>
<td>Normal histology</td>
<td>12.2</td>
<td>13.4</td>
<td>.73</td>
</tr>
<tr>
<td>Normal endoscopy/histology</td>
<td>9.5</td>
<td>10.7</td>
<td>.76</td>
</tr>
</tbody>
</table>
Ulkus-lignende dyspepsi  N=39

Refluks-lignende dyspepsi  N=120

Dysmotilitets-lignende dyspepsi  N=219
PAPER 1
Towards a true prevalence of peptic ulcer: the Sørreisa gastrointestinal disorder study

B Bernersen, R Johnsen, B Straume, P G Burhol, T G Jenssen, P A Stakkevold

Abstract
This study, designed to overcome methodological problems inherent in earlier prevalence studies of peptic ulcer, was carried out in a municipality in northern Norway. It included the total population of 2077, aged 20-69 years, and comprised a questionnaire and search for previously diagnosed peptic ulcers in the local medical records for all subjects, and additional endoscopy of all subjects with dyspepsia and their matched healthy controls (n=619). The overall prevalence was 15-5% in men and 9-5% in women, a sex ratio close to one and a higher duodenal:gastric ratio than previously reported from this region. A substantial 1% prevalence of asymptomatic ulcers was also observed.

Tell me, sweet Lord, what is that takes from thee thy stomach, pleasure, and thy golden sleep?" says Lady Percy to her husband Henry. Not only does classical literature, like Shakespeare's Henry IV, link gastric disorders to men, medical reports also identify peptic ulcer as a male infirmity.

During the past 40 years, studies have consistently shown higher prevalences in men for both gastric and duodenal ulcer.\(^1\) Kurata, however, has reported a decline in sex ratio of self-reported peptic ulcers in the USA to 1:1.\(^2\) The prevalence of duodenal ulcer seems to vary considerably around the world, but it generally occurs more frequently than gastric ulcer.\(^3\) Studies in Scandinavia have shown gastric ulcer to be more common than duodenal ulcer in the northern part,\(^4\) whereas duodenal ulcer dominates in the southern part.\(^5\) Only one study from Malmo in southern Sweden, which was based on necropsy examinations, showed a higher prevalence of gastric than duodenal ulcer in both men and women.\(^6\)

Studies on the occurrence of peptic ulcer that use patients' records are hampered by considerable biases. Selection takes place both by patients with dyspepsia deciding whether or not to present their problems to the physician and by physicians deciding whether to refer their patients for further diagnostic procedures. Moreover, surveys where the diagnosis of peptic ulcer depends on symptoms are complicated by the fact that some peptic ulcers are asymptomatic.\(^7\)

The purpose of this population based study was to establish an overall prevalence of peptic ulcer, both for symptomatic and for asymptomatic ulcers, by combining a lifetime prevalence from questionnaire reports and examination of available medical records together with a point prevalence from endoscopy of subjects both with and without dyspepsia. The study endeavoured to get closer to the true prevalence of peptic ulcer disease.

Material and methods
This study was carried out in the municipality of Sørreisa in northern Norway (latitude, 69° north). The town has 3500 inhabitants and is in a rural area with a local administration centre. The principal occupations are agriculture and wood-processing and service industries, a distribution of occupational groups close to the average for Norway. From March to May 1987 all inhabitants born between 1917 and 1967, 2077 men and women, received a postal questionnaire with 119 questions on abdominal complaints, health, lifestyle, diet, and social conditions.

Subjects with positive responses to the first two or the last of the following questions, or both, were considered to have suffered dyspepsia:

Have you ever had abdominal pain of at least two weeks' duration?

If yes, was the pain located to the upper abdomen?

Have you ever had heartburn or acid regurgitation almost daily for at least one week?

Those who had had dyspepsia but no prior history of peptic ulcer, gall stone, kidney stone, cardiac diseases, or abdominal surgery were offered endoscopy. Corresponding asymptomatic controls matched for sex and age (within the same 10 year age group) were randomly selected and offered an endoscopy as well. Controls who refused endoscopy were replaced by a second, similar procedure. Ten pregnant women were excluded from endoscopy, and in the following analysis they were included in the refuser group.

The Figure summarizes the study procedures. Of 495 subjects with dyspepsia, 137 were excluded. Of 782 subjects invited to have endoscopy, 309 dyspepsics and 310 controls underwent gastroscopy. The subjects were endoscoped within one month of returning their questionnaires, and after first giving their informed consent.

All endoscopies were performed by one of the authors (BB), who is a trained endoscopist. The examinations were carried out at the local health centre with Olympus gastrosopes GIF Type Q 20. The endoscopist was blinded in the sense of not knowing whether or not he was examining subjects with dyspepsia or controls.

A gastric or a duodenal ulcer was diagnosed if an ulceration greater than 0-5 cm was seen proximally or distally to the pylorus, respectively. Deformity of the duodenal bulb was considered to be present when flattening, scars, atrophy, or narrowing of the bulb was seen.
Biopsy specimens were taken from both the greater and lesser curvatures of the corpus and antrum of the stomach, from the proximal and distal parts of the duodenum, and also from all regions. The specimens for histological examination were prepared and interpreted by the Department of Histopathology at the University of London. Finally, the medical records for the total population were examined for evidence of previously diagnosed peptic ulcers confirmed by barium studies or endoscopy.

Table 1 shows the distribution of the total population and subpopulations by sex and 10 year age groups. Differences in sex and age distribution between the total population and the subpopulations were evaluated by the Chi-square test. Population estimates of point prevalences of peptic ulcer were calculated from the gastroscopic findings adjusted for sex and age by analysis of covariance. In this calculation the prevalence rates of controls were used for the non-respondent group. The overall prevalences in the total population are based on these population estimates and the figures from the record verification procedure.

**Table 1**: Sex-specific prevalence of self-reported and re-verified gastric, duodenal, and peptic ulcer in 1035 men and 992 women aged 20–69 (Sorvella 1987)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Reported peptic ulcer</td>
<td>59</td>
<td>6.5</td>
</tr>
<tr>
<td>Not confirmed by records</td>
<td>9</td>
<td>1.2</td>
</tr>
<tr>
<td>Verified peptic ulcer</td>
<td>50</td>
<td>5.9</td>
</tr>
<tr>
<td>False negatives</td>
<td>11</td>
<td>1.3</td>
</tr>
<tr>
<td>Ulcers among non-responders</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Total peptic ulcer</td>
<td>64</td>
<td>7.0</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>14</td>
<td>1.5</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>35</td>
<td>3.6</td>
</tr>
<tr>
<td>Combined ulcers</td>
<td>1</td>
<td>0.1</td>
</tr>
<tr>
<td>Unknown location</td>
<td>2</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Confidence intervals based on the Poisson distribution are given when presenting the prevalences of ulcers in the total population. The 95% confidence intervals indicate the random variation due to the sampling fractions of subjects with and without dyspepsia in the Sorvella population only. Therefore, only the point estimates apply to a universe population.

The study was approved by the local ethics review board.

**Results**

Some 1802 of 2027 (88.9%) people returned the questionnaire (Figure). One hundred and three people were excluded because of an earlier diagnosis of peptic ulcer in 89, coronary heart disease in 33, and gall stones or kidney stones in 15. Three hundred and nine of the 358 subjects were eligible for examination endoscopy, and 309 attended for examination endoscopy together with 310 of the 424 matched controls. Therefore 79.2% of those invited to endoscopy participated. Of the 163 refusals, 114 were controls.

There were no significant differences in the sex distribution within the populations. Compared with the total population, middle-aged men and women were slightly over-represented among those undergoing endoscopy. Female non-responders and refusals for endoscopy were significantly younger when compared with the total population. The median age of subjects with dyspepsia was 40-5 years (range: 20-69) and that of controls was 40-5 years (range: 20-68).

The results from examination of the medical records are presented in Table 1. No medical records were found for 103 of the subjects (5.1%), 12 of whom belonged to the endoscopy population without peptic ulcer. Medical records were found for all those who reported previous peptic ulcer, and they showed a false positive rate of reporting of 15-5% in men and 20.0% in women. Corresponding false negative rates of reporting were 1-3% and 0-2%, respectively. When four subjects with peptic ulcer were included among the non-responders, the lifetime prevalences of peptic ulcer were 6.2% in men and 2.7% in women, giving a male/female ratio of 3:1 and a duodenal/gastric ulcer ratio of 3:2:1 and 1:3:1 for men and women respectively.

Table III shows endoscopy results in both subjects with dyspepsia and control subjects. The presented prevalences are adjusted for age distribution.

**Table 2**: Sex-specific percentage age distribution of total population, questionnaire responders and non-responders, subjects endoscoped and subjects refusing endoscopy (Sorvella 1987)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Total Population</th>
<th>Men</th>
<th>Women</th>
<th>Questionnaire responders</th>
<th>Men</th>
<th>Women</th>
<th>Subjects endoscoped</th>
<th>Men</th>
<th>Women</th>
<th>Subjects refusing endoscopy</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>30–39</td>
<td>27 1</td>
<td>21 2</td>
<td>6 6</td>
<td>20 9</td>
<td>15 9</td>
<td>18 11</td>
<td>13 9</td>
<td>12 11</td>
<td>18 11</td>
<td>13 9</td>
<td>12 11</td>
<td>18 11</td>
</tr>
<tr>
<td>50–60</td>
<td>19 16</td>
<td>16 10</td>
<td>5 14</td>
<td>13 14</td>
<td>9 14</td>
<td>12 14</td>
<td>10 14</td>
<td>9 14</td>
<td>12 14</td>
<td>10 14</td>
<td>9 14</td>
<td>12 14</td>
</tr>
<tr>
<td>60–69</td>
<td>13 11</td>
<td>10 9</td>
<td>3 12</td>
<td>10 12</td>
<td>8 12</td>
<td>10 12</td>
<td>10 12</td>
<td>8 12</td>
<td>10 12</td>
<td>10 12</td>
<td>8 12</td>
<td>10 12</td>
</tr>
</tbody>
</table>

Significant differences in distribution of age compared with total population by **p<0.01**. **p<0.001**.
distribution in the total population. Except for
gastric ulcers in subjects with dyspepsia, we
found higher point prevalences for peptic ulcers
and deformed duodenal bulbs in women. The
mean age of subjects with peptic ulcers was 45-8
years for men and 45-6 years for women. In the
calculation of the number of expected peptic ulcers in the total population, we used the ageadjusted prevalences for each ulcer localization, total peptic ulcers, and deformed duodenal bulbs separately. Because of this the sum of the gastric
and duodenal ulcers does not always correspond
with the total number of peptic ulcers. Using ageadjusted prevalences rather than the corresponding crude prevalences increased the number of peptic ulcers by one in both sexes and the
number of deformed duodenal bulbs by one in
men and two in women. The male:female ratio
for calculated total peptic ulcer then became 0.7:1, irrespective of whether deformed duodenal
bulbs were included or not. The duodenal:gastric ulcer ratio was 2:3:1 in men, and 1:3:1 in
women.

Table IV gives the overall prevalences in the
total population. The 95% confidence limits,
using the Poisson distribution, represent the estimated intervals of prevalence in any population comparable with that of Sorrosa. The prevalence of 7.4% for peptic ulcer in men was
significantly higher than that for women (4.6%).
When deformed duodenal bulbs were included in the peptic ulcer group, however, this difference disappeared, giving an overall prevalence of 10.3% in men and of 9.5% in women.

Discussion
This study was carried out in a well defined
population and attracted a high response rate.
The study also included blind endoscopy of all
subjects with dyspepsia who agreed to the
examination as well as of matched healthy
controls. In addition we included a search for
previously diagnosed peptic ulcers in the local
medical records of all subjects who received a
questionnaire. The study was designed to
eliminate some of the major methodological
problems inherent in most prevalence studies on
peptic ulcer. To our knowledge, no previous
study on peptic ulcer prevalence has used a
similar design. Our main findings of a high
overall prevalence, a sex ratio close to one, a
somewhat unexpected duodenal:gastric ulcer ratio, and a high prevalence of asymptomatic ulcers may mainly be ascribed to our study design.

Table III. Observed numbers and prevalences (%) of gastric ulcer (GU), duodenal ulcer (DU), total peptic ulcer (PU), and deformed duodenal bulb (DDB) found by endoscopy in 339 men and 280 women, aged 20-69 years. Calculated numbers (X) of peptic ulcers for the respective populations are presented. (Sorrosa 1987)

<table>
<thead>
<tr>
<th>Ulcer Type</th>
<th>Men (n=100)</th>
<th>Women (n=90)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>GU</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>DU</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>PU</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>DDB</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

*Prevalence (%) adjusted for age distribution in the local population.

Life-time prevalences for peptic ulcer in previous surveys vary from 5-6% in men and
1.9 to 6.0% in women. Necropsy studies, on the other hand, have shown considerably
higher prevalences, varying from 18.4 to 20.9% in men and from 9.5 to 14.7% in women. Unfortunately, the occurrence of peptic ulcer caused by terminal illnesses is unknown, and since most necropsy populations are highly
selected, any comparison with prevalence
studies on healthy subjects is questionable.

Our estimated overall prevalences of peptic ulcer disease of 10.3% in men and 9.5% in
women are higher than those previously reported for men and even more so for women.

Most prevalence and incidence studies of peptic ulcer have been in patient populations
where selection is biased by both the patient's
and the doctor's decisions. Even in population based studies, the diagnostic procedures have
mainly included subjects with severe symptoms, thereby excluding those with minor or no
complaints. We have avoided these biases by offering endoscopy to all subjects with dyspepsia together with healthy matched control subjects.

Most surveys have reported that peptic ulcer disease is two to four times more frequent in
men than in women, but the male:female ratio
varies with both age and ulcer location. It may
thus approach 1:1 ratio according to Kurihara,
and also to Doll and Banke in those above 55
years of age. In a follow up study of 174
patients with non-ulcer dyspepsia, Krag found
that 59% of the men and 42% of the women
subsequently developed a peptic ulcer. The
male:female ratio of 0.7:1 in the estimated point
prevalences of peptic ulcers contrasts with both
the corresponding ratio of previously diagnosed peptic ulcers in this population and with those
reported in other studies. The number of
peptic ulcers found by endoscopy was small, but
the same sex distribution was found among the
considerably larger number of deformed duodenal bulbs. These findings indicate that peptic
ulcer has been underdiagnosed in women in our
population, and this may also be the case in other
studies on patient populations. This could partly
be due to asymptomatic ulcers, but even among
the subjects with dyspepsia, women had more
peptic ulcers. The idea that peptic ulcer is mainly
a male disease may have led to a higher diagnostic
intensity in men.

In the USA and Europe, duodenal ulcer
usually occurs in men, with a higher frequency
as

<table>
<thead>
<tr>
<th>Ulcer Type</th>
<th>Men (n=1035)</th>
<th>Women (n=992)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>CI</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1.7 (1.6-2.1)</td>
<td>2.0 (1.5-2.6)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>2.9 (2.5-3.3)</td>
<td>2.6 (2.0-3.2)</td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>7.4 (6.9-8.2)</td>
<td>4.6 (3.8-5.5)</td>
</tr>
<tr>
<td>Peptic ulcer inclusive of DDB</td>
<td>10.9 (9.5-11.9)</td>
<td>9.5 (7.9-11.2)</td>
</tr>
</tbody>
</table>

*Combined figures from the endoscopy study and the record verification procedure.
Based on Poisson distribution.

No significant difference in ulcer localization between the sexes.
Previous studies in northern Norway have shown higher prevalences and incidences of gastric than duodenal ulcer. In southern Norway, on the other hand, Knutsen and Selvaag found a duodenal:gastric ulcer ratio of 1.8.5:1. In Denmark, incidence rates in patient populations are some four times higher than duodenal (0.13%) compared to gastric ulcer (0.03%).

One Norwegian study concluded that gastric ulcer relapses are often asymptomatic, but to our knowledge there are no published studies on prevalences of asymptomatic peptic ulcer. Point prevalences of 1.0% for peptic ulcers and 3.2% for duodenal bulb ulcer among controls in this study indicate that asymptomatic peptic ulcers are common.

In our estimation of the overall prevalences we have treated those who did not respond to our questionnaire as control subjects. An alternative estimation, where the non-responders were given the point prevalence of subjects with dyspepsia, left the overall prevalence almost unchanged.

All but 12 primary health records of those who underwent endoscopy were found and examined. No information on previous peptic ulcer was found, corresponding with the answers in the questionnaire. This indicates that the peptic ulcers found by endoscopy were first time peptic ulcers.

Despite the comprehensive design of this study, we still cannot account for several potential methodological problems. The unknown rate of tears from previous peptic ulcers and the unknown duration and incidences of asymptomatic and barely symptomatic peptic ulcers represent our major sources of uncertainty. All of these areas of insufficient knowledge with their corresponding flaws in almost any study design probably lead to a considerable underestimation of the true prevalence of peptic ulcer.

In conclusion, we claim that asymptomatic peptic ulcers are quite common, and even that the high overall prevalences found in this study must be regarded as minimum figures. Finally, we question the current opinion on the sex ratio of peptic ulcer disease.
PAPER II
Non-ulcer dyspepsia and peptic ulcer: the distribution in a population and their relation to risk factors

The Sorrento gastro-intestinal disorder study.
B Bernarsen, R Johnsen, B Straume

Abstract

Background—The aetiology of non-ulcer dyspepsia and a possible connection to peptic ulcer disease is debated. This paper discusses this problem in a population based study.

Aims—The relation between non-ulcer dyspepsia and peptic ulcer disease was explored by the distribution in the general population and their associations to demographic, lifestyle, and psychological factors.

Methods—All inhabitants of a community aged 20–69 years received a questionnaire concerning abdominal complaints, health, lifestyle, diet, and social conditions. Reports on peptic ulcer were verified with medical records. Dyspeptic subjects and matched healthy, non-dyspeptic controls were endoscoped in a blinded procedure.

Subjects—Of 2027 persons invited, 1892 (88.9%) returned the questionnaire from which dyspeptic subjects and controls were identified. Of 782 subjects invited to endoscopy, 509 dyspeptic and 310 control subjects (79.2%), participated.

Results—Men reported dyspepsia (30.4%) and peptic ulcer (8.7%) more often than women (24.1% and 5.2%, respectively). Non-ulcer dyspepsia was frequent (between 10.6% and 17.2%) in both sexes and age groups up to 60 years, with a lower frequency in both men and women above this age (3.0% and 6.8%). Non-ulcer dyspepsia was associated with having a family history of dyspepsia and of peptic ulcer and the use of tranquilisers. Nearly one third of dyspeptic persons above the age of 40 years had peptic ulcer, but peptic ulcer prevalence was low under this age. Peptic ulcer was associated with a family history of peptic ulcer, smoking, and daily life stress, and also with poor living conditions during childhood, frequent recurrence of herpes labialis, conditions that were associated with Helicobacter pylori infection.

Conclusions—Non-ulcer dyspepsia and peptic ulcer have different patterns of relations to lifestyle, social, and psychological factors. The results perhaps support the hypothesis of peptic ulcer being an infectious disease in contrast with non-ulcer dyspepsia.

(Orig 1996; 38: 823–829)

Keywords: dyspepsia, peptic ulcer, population study, Helicobacter pylori, lifestyle.

It is usual that about one third of dyspeptic patients claim to have peptic ulcer disease. The frequency of ‘unexplained’ dyspepsia depends, however, on the selection of patients. While Gregory et al found that only three of 102 dyspeptic patients in general practice developed a peptic ulcer,1 Kragh found this in 10% of hospitalised patients.

Our study on peptic ulcer disease and non-ulcer dyspepsia in a large population has shown that these conditions had substantially different relations to psychological, social, lifestyle, and dietary variables. Peptic ulcer was strongly associated with age, a family history of peptic ulcer, body mass index, and smoking, whereas non-ulcer dyspepsia was associated with psychological factors and social conditions. In this large population study, however, the diagnoses were not verified. A population based case control study of risk factors in prepyloric and duodenal ulcer patients and controls gave no support to the concept that peptic ulcer disease is a disorder related to psychological stress.

Are peptic ulcer disease and non-ulcer dyspepsia, despite similar symptoms, aetologically and pathogenetically different conditions? To elucidate the relation between non-ulcer dyspepsia and peptic ulcer disease, we have studied their distribution in a general population and their associations to possible aetiological factors.

Methods

From March to May 1987 all inhabitants of the municipality of Sorrento in northern Norway aged 20 to 69 years, 2027 men and women, received a postal questionnaire with questions concerning abdominal complaints, health, lifestyle, diet, and social conditions. Of 2027 persons invited, 1892 (88.9%) returned the questionnaire. The inhabitants of this municipality have all their medical contacts with one of the two family physicians at the one and only local health service centre, and their hospital services from the one and only regional hospital. All reports of a previously diagnosed peptic ulcer, were verified by searching individual medical records, which were easily identified in the local health service centre or at the regional hospital.

All subjects giving affirmative answers to the first two or the last of the following questions were considered dyspeptic patients: ‘Have you ever had abdominal pain of at least two weeks duration?’, ‘If yes, was the pain located in the upper abdomen?’ and ‘Have you ever had
heartburn or acid regurgitation almost daily during at least one week. Of 495 dyspeptic persons, 89 subjects reporting a prior history of peptic ulcer, 15 subjects reporting gall stones or kidney stones, and 33 reporting coronary heart disease, were all excluded. The remaining 354 persons were offered an endoscopy free of charge but without any reward. Healthy, non-dyspeptic controls matched for sex and age within the same 10-year age group, were randomly selected and offered an endoscopy as well. The controls were selected from the questionnaire survey, as they reported that they never had experienced abdominal pain at any location or heartburn or acid regurgitation and that they never had consulted their general practitioner with dyspepsia. Of 782 subjects invited to endoscopy, 619 (79.2%) attended, of whom 309 were dyspeptic subjects and 310 controls. All subjects were endoscoped within one month after returning the questionnaire. After completing the verification procedure searching all local medical records for confirmation of a previous peptic ulcer and after endoscoping the 619 persons, 409 persons, of the initial 495 persons, reporting dyspepsia were without a previous or present peptic ulcer. A detailed description of the methods has been published elsewhere. The study was approved by the Regional Committee for Medical Research Ethics.

Endoscopy study
All endoscopies were performed by one of the authors (BB), who is a trained endoscopist. The endoscopist was masked to whether he examined a dyspeptic or a non-dyspeptic person. A gastric or duodenal ulcer was diagnosed if an ulceration greater than 0.5 cm was seen proximally or distally to the pyloris, respectively. Deformity of the duodenal bulb was considered to be present when flattening, scars, stenosis, or narrowing of the bulb was seen. Endoscopic duodenitis was diagnosed according to the criteria of Vennells.

Biopsy specimens for histological diagnosis were taken from all lesions. Stomach biopsy specimens for Helicobacter pylori cultures, were placed in 0.5 ml of glucose/saline solution (25% glucose in 0.9% saline solution), ground, and dispersed on blood agar and on brain-heart infusion agar containing horse (5% v/v) blood within five minutes after endoscopy.

Definition of groups for analysis
Dyspeptic group - All persons with dyspepsia as defined above, but without a present or previous peptic ulcer.
Non-ulcer dyspepsia - All dyspeptic subject attending the endoscopic study without peptic ulcer, deformity of the duodenal bulb, endoscopic duodenitis of the duodenal bulb.
Peptic ulcer - All persons with peptic ulcer verified with any of the medical records and persons having a peptic ulcer or an ulcer scar (deformed duodenal bulb) at the endoscopy.
Reference population - In the logistic regression analysis of dyspepsia, non-ulcer dyspepsia, and peptic ulcer, the reference population comprised subjects without any of the mentioned conditions.

Regression analyses
The following independent variables were explored and finally assessed in a logistic regression: age; sex; daily smoking (yes/no); number of cigarettes smoked daily; previous smoking (yes/no); coffee consumption (no less than 1 cup a day, 1-2 cups, and 6 cups or more a day); beer, wine, and liquor consumption (0-2); relationship as being married (mother's milk or not), regularity of medication, excessive use of spices, ketchup or mustard, use of some specific drugs (aspirin, non-steroidal anti-inflammatory drugs, sleep aids) and tranquilizers, shift work (yes/no), social stress (four categories, never to all the time); physical activity at leisure time (grade 0-4: sedentary, moderate, active, and hard training); living conditions during childhood (four categories, from very bad to very good), and dyspepsia or peptic ulcer, or both in the family (first degree relatives); bothered by herpes labialis (four categories, never to very frequent); reporting complaint as frequent headache, unspecific vertigo, palpitations and insomnia, where reporting more or less than three of these symptoms, respectively, were graded as yes/no.

Statistical methods
Age trends were tested by Mantel-Haenszel test. Logistic regression and adjustment for age and sex distribution by analysis of covariance were made in the SPSSX statistical program.

Results
Table I shows the prevalences of reported dyspepsia, non-ulcer dyspepsia, and peptic ulcer. Of the 309 persons with dyspepsia endoscoped, 31 had a peptic ulcer or a deformity of the duodenal bulb at the present time and 42 had an endoscopic duodenitis, leaving 236 persons with non-ulcer dyspepsia.

There were no significant differences in frequency of dyspepsia between the two sexes when stratified for age, but there was a slight increasing trend with age in the frequency of dyspepsia in men (p=0.003). The prevalences of non-ulcer dyspepsia did not differ between the sexes and seemed stable throughout the ages.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>Dyspepsia (n=409)</th>
<th>Non-ulcer dyspepsia (n=333)</th>
<th>Peptic ulcer (n=136)</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-39</td>
<td>235</td>
<td>193</td>
<td>106</td>
<td>14</td>
</tr>
<tr>
<td>30-39</td>
<td>200</td>
<td>222</td>
<td>100</td>
<td>14</td>
</tr>
<tr>
<td>40-49</td>
<td>292</td>
<td>189</td>
<td>122</td>
<td>14</td>
</tr>
<tr>
<td>50-59</td>
<td>133</td>
<td>125</td>
<td>133</td>
<td>12</td>
</tr>
<tr>
<td>60-69</td>
<td>141</td>
<td>162</td>
<td>113</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>905</td>
<td>897</td>
<td>672</td>
<td>87</td>
</tr>
</tbody>
</table>
age span, only showing a pronounced decrease in the age group above 60 years. Peptic ulcer had a significant sex difference with more diagnosed peptic ulcers in men (p = 0.002) and an increasing prevalence with age for both sexes (p < 0.0001) with a pronounced increase in men aged over 40 years and women aged over 50 years.

Table II shows the results of the regression analysis. A corresponding analysis of dyspepsia excluding persons reporting irritable bowel symptoms according to Manning's criteria, gave mainly the same results as presented for dyspepsia. The non-ulcer dyspepsia group, consisting of the subjects with dyspepsia in the endoscopy population when excluding organic pathological endoscopic findings, had chiefly the same relations as the dyspepsia group, but in addition showed a significant association with use of tranquillisers. The analysis of non-ulcer dyspepsia contrasted with the matched controls gave the same relations (with a somewhat lower strength).

Finally, in persons with peptic ulcer disease, there were significant contributions from age, sex, family history of peptic ulcer, smoking, previous smoking, tea drinking, frequent recurrences of herpes labialis, breast fed as a baby, poor living conditions during childhood, and the feeling of lack of time.

In an analysis of the endoscopy persons, H. pylori infection was found in 49.6% of subjects having frequent recurrences of herpes labialis, while subjects never or seldom having this condition were infected in 39.7% (p = 0.04). Subjects having poor living conditions during their childhood were infected with H. pylori in 49.6%, while subjects having good or fair living conditions during their childhood had this infection in 37.3% (p = 0.003).

Discussion

Dyspepsia is a common disorder, even when symptoms are restricted to upper abdominal pain or heartburn or acid regurgitation of at least two weeks' duration as in this study. We found that men were more likely to be afflicted with dyspepsia, with a small increase with age, unlike women. Non-ulcer dyspepsia occurred with a similar frequency in both sexes up to 60 years, but was less common in older people of both sexes. Peptic ulcer was seldom found up to the age of 40 years in men and 50 years in women, but in older dyspeptic patients nearly one third had a peptic ulcer.

Dyspepsia has been defined and classified in various ways, but in this study the definition includes the most commonly accepted symptoms with a low grade of selection on severity and duration. In our definition of non-ulcer dyspepsia, we have chosen to exclude both peptic ulcer, ulcer scars (atrophy), and endoscopic duodenitis of the duodenal bulb.

Our investigation shows that relations to background factors were quite similar for dyspepsia and non-ulcer dyspepsia, the only difference was that patients with non-ulcer dyspepsia were treated, for example with reduction of coffee drinking and use of tranquillisers. In epidemiological studies there are few reasons to differentiate between dyspepsia and non-ulcer dyspepsia.

Non-ulcer dyspepsia was associated with a family history of peptic ulcer and also with a family history of dyspepsia. To our knowledge, there are no theories of inheritance of dyspepsia, but dyspeptic symptoms may be inherited by learning habits and how to report them. Our finding of a relation to previous smoking in dyspeptic subjects similar to the association between peptic ulcer and tea drinking, may be seen as a result of changed habits related to the disease.

We know of no previous reports on associations between tea drinking and peptic ulcer and this finding may be a spurious one or is due to changed habits among peptic ulcer patients because of medical counselling. Tea drinkers controlled for earlier coffee drinking showed that 38% of dyspeptic subjects and 21% of non-dyspeptic subjects had stopped coffee drinking.

Pepitic ulcer has in this study a quite different pattern of relations, firstly to age and sex, but also to well known factors as smoking and a family history of peptic ulcer. For peptic ulcer this last relation may fit in with theories of inheritance, but also with family clustering of H. pylori. The relations to frequent recurrences of herpes labialis may indicate a connection to infectious diseases. We found an association between frequent herpes labialis recurrences and H. pylori infection. Duodenal ulcer has earlier been connected to herpes virus

**Table II** Odds ratio (OR) of the independent variables in a logistic regression analysis among 1802 men and women with dyspepsia (n = 1789), non-ulcer dyspepsia (n = 256), and peptic ulcer (n = 132) in contrast with the reference population (n = 1267). Stockholm 1987

<table>
<thead>
<tr>
<th>Independent variable</th>
<th>Dyspepsia (n = 1789)</th>
<th>Non-ulcer dyspepsia (n = 256)</th>
<th>Peptic ulcer (n = 132)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>OR</td>
<td>OR</td>
</tr>
<tr>
<td>Total age group</td>
<td>1.02</td>
<td>0.93 to 1.14</td>
<td>1.90</td>
</tr>
<tr>
<td>Sex (male, female)</td>
<td>1.53</td>
<td>1.09 to 2.14</td>
<td>1.10</td>
</tr>
<tr>
<td>Family history of dyspepsis (mothers)</td>
<td>1.21</td>
<td>1.03 to 1.42</td>
<td>1.10</td>
</tr>
<tr>
<td>Peptic ulcer in the family (mothers)</td>
<td>1.35</td>
<td>1.04 to 1.78</td>
<td>1.21</td>
</tr>
<tr>
<td>Smoking (mothers)</td>
<td>1.69</td>
<td>1.27 to 2.26</td>
<td>1.46</td>
</tr>
<tr>
<td>Previous smoking (mothers)</td>
<td>1.98</td>
<td>1.45 to 2.70</td>
<td>1.58</td>
</tr>
<tr>
<td>Tea drinking (mothers)</td>
<td>1.15</td>
<td>0.90 to 1.46</td>
<td>1.36</td>
</tr>
<tr>
<td>Frequent herpes labialis (mothers)</td>
<td>1.10</td>
<td>0.95 to 1.26</td>
<td>1.27</td>
</tr>
<tr>
<td>Breast feeding as baby (mothers)</td>
<td>1.01</td>
<td>0.77 to 1.32</td>
<td>1.39</td>
</tr>
<tr>
<td>Frequent complaints (mothers)</td>
<td>1.16</td>
<td>0.90 to 1.48</td>
<td>1.29</td>
</tr>
<tr>
<td>Use of tranquillisers (mothers)</td>
<td>1.56</td>
<td>1.23 to 1.98</td>
<td>1.27</td>
</tr>
<tr>
<td>Feeling of lack of time (mothers)</td>
<td>1.13</td>
<td>0.98 to 1.31</td>
<td>1.23</td>
</tr>
<tr>
<td>Poor living conditions during childhood (mothers)</td>
<td>1.15</td>
<td>0.98 to 1.40</td>
<td>1.22</td>
</tr>
</tbody>
</table>

*p < .05 - confidence intervals.
infection and a theory proposing that duodenal ulcer could be of herpetic origin. We did not expect that being breast fed as baby would be associated with peptic ulcer. We found no relation between *H. pylori* infection and breast feeding as baby in this study and to our knowledge no data connecting these conditions exist. The relation is weak, and this finding should be interpreted with caution. Poor living conditions during childhood have been connected with low resistance against other diseases, but may also be connected with early infection of *H. pylori*. In our endoscopy group subjects with poor living conditions during their childhood had *H. pylori* infection significantly more often than those better off during their childhood. It may be hypothesized from these data that several preventive risk factors for peptic ulcer are spurious and express an association with infective agents as *H. pylori*.

Regardless of the different pattern of relations to background factors between peptic ulcer and dyspepsia, the clinician will always ask when dyspepsia represents peptic ulcer or not. It would be financially worthwhile to carry out an endoscopy or a breath test diagnosing *H. pylori* infection. In our population study, the *H. pylori* status was obtained in all persons who had an endoscopy, dyspeptic as well as non-dyspeptic controls. From these data it is obvious that a positive *H. pylori* diagnosis did not tell us whether a dyspeptic person has a peptic ulcer or not. The question is whether or not the non-ulcerous mucosa will help the practitioner to decide what advice and what treatment to give. At least, the low occurrence of peptic ulcer among young people support a reluctant attitude towards endoscopy of young dyspeptic patients.

The results in this study may be questioned because of the comparatively small numbers for all groups studied. The cross sectional design does not allow us to make conclusive inferences on causality. Furthermore, we do not have data on the *H. pylori* occurrence in our total study group, only in the 619 subjects endoscoped. These disadvantages may to some extent be compensated by our comprehensive investigations to verify reported ulcers as most studies on peptic ulcer in studies with larger numbers are burdened with diagnostic problems. The 'blinding' of the endoscopy of all dyspeptic subjects and controls will also reduce the possibility of biased findings.

We conclude that non-ulcer dyspepsia and peptic ulcer have different patterns of relation to lifestyle, social, and psychological factors. The results of this study seem, with some reservations, to support the hypothesis of peptic ulcer being an infectious disease in contrast to non-ulcer dyspepsia.
PAPER III
PAPERS

Prevalences of endoscopic and histological findings in subjects with and without dyspepsia

Roar Johnsen, Bjørn Berntsen, Bjørn Straume, Olav Helge Førde, Leif Bostad, Per G Burhol

Abstract

Objective—To examine the association between dyspeptic symptoms and endoscopic and histological diagnoses.

Design—Cross sectional study of people with dyspepsia and controls matched for age and sex identified by questionnaire survey of all inhabitants aged 20 to 69. Endoscopy and histological examination was performed with the examiner blind to whether or not the patient had dyspepsia.


Subjects—All people with dyspepsia and age and sex matched people without dyspepsia were offered endoscopy. A total of 209 people with dyspepsia and 310 without dyspepsia underwent endoscopy, giving 223 matched pairs.

Main outcome measures—Prevalences of endoscopic and histological diagnoses made according to internationally accepted standards.

Results—In all, 1802 of 2027 (88.9%) people returned the questionnaire. Of the 163 subjects who refused endoscopy, 114 were controls. Of five endoscopic and four histological diagnoses only peptic ulcer disease, endoscopic duodenitis, and active chronic gastritis were diagnosed significantly more often in people with dyspepsia. In all, 30% to 50% of the diagnoses of mucosal inflammation and peptic ulcer disease were made among subjects without dyspepsia, and only 10% of both those with and those without dyspepsia had normal endoscopic findings.

Conclusions—The diagnostic findings, with possible exceptions of peptic ulcer disease and endoscopic duodenitis, showed no association of clinical value with dyspeptic symptoms. The small number of "normal" endoscopic findings in both those with and those without dyspepsia challenge well accepted endoscopic and histological diagnostic criteria with relation to the upper gastrointestinal tract.

Introduction

The disability, suffering, and health care resources associated with patients in whom disease is wrongly suspected represent a mounting burden in modern medicine and permanently challenge our ability to recognize normality and discriminate between disease and "non-disease."

In gastroenterology the controversy around the "dyspeptic myth" of gastroduodenitis is one of many examples of this problem. So far the discussion on gastroduodenitis has mainly focused on the association with dyspepsia and peptic ulcer disease. Studies on the occurrence of this condition among people without dyspepsia, which could have settled parts of the controversy, have been scarce and based on small populations.1 The lack of agreement on what symptoms should be included in the term "dyspepsia" may likewise have nourished the controversy.

A working party of gastroenterologists defined dyspepsia as any symptom "considered to be referred to the proximal alimentary tract," while others have restricted the term to chronic or recurrent abdominal pain or nausea, or abdominal symptoms, often relating to feeding.2 Any population of people with dyspepsia selected according to these definitions could vary considerably regarding both the character of single symptoms and that of complexes of symptoms.

Most studies of patient populations with different prevalences of peptic ulcer disease are inconclusive regarding the relation between chronic gastritis and dyspepsia and peptic ulcer disease. The few population studies on chronic gastritis reject any association with dyspepsia and question an association with peptic ulcer disease.3−5 Corresponding surveys on duodenitis are not available, and the discussion on whether endoscopic and histological duodenitis represents the same disorder and is part of the range of peptic ulcer disease is based on patient surveys and a few studies in healthy volunteers.6−8

A discussion on normality and the clinical value of dyspeptic symptoms associated with different conditions in the upper gastrointestinal tract can be assessed only from population based studies. Despite common agreement on the diagnostic criteria of stages of different pathological conditions in the upper gastrointestinal tract,9−11 a main problem in all of the studies is the observer bias related to the knowledge whether or not the patient has symptoms. To achieve a non-biased assessment of the clinical value of dyspeptic symptoms we performed endoscopy in subjects with and without dyspepsia, and with the examiner being unaware of whether or not the subject has symptoms.

Methods

After a population based questionnaire survey of inhabitants aged 20-69 years in the municipality of Sørreisa in northern Norway (n=2027) all subjects reporting dyspepsia and matched subjects without dyspepsia were offered endoscopy of the upper gastrointestinal tract. There was no financial gain or harm, and health benefits associated with the invitation. Subjects with dyspepsia were selected on the basis of answers to the first two or the last, or both, of the three questions: "Have you ever had abdominal pain of at least two weeks' duration?"; "If yes, was the pain located to the upper abdomen?"; and "Have you had heartburn or acid regurgitation almost daily for at least one week?"

Subjects with dyspepsia who reported a history of peptic ulcer, abdominal surgery, gall stones, kidney stones, or cardiac disease were excluded. For other subjects, exclusion criteria were: drug use potentially affecting endoscopic appearance, or alcohol intake exceeding 10 units per week, or a previous upper gastrointestinal endoscopy. The study was approved by the regional ethical committee.
Biopsy specimens were obtained from the corpus and antral part of the stomach, including both the greater and lesser curvatures; from the proximal and distal parts of the duodenum; and from all visible lesions. The specimens for morphological examination were prepared according to standard methods and interpreted blindly by an experienced pathologist (I.B.). Inflammation of gastric and duodenal mucosae was classified according to Whitehead et al. and Owen. The study was approved by the regional committee of medical research ethics.

**Results**

Some 1802 of 2027 (88.9%) subjects returned the questionnaire. Of the 163 subjects who refused endoscopy, 114 were controls. There were no significant differences in the sex distribution between responders and non-responders and between subjects who had endoscopy and those who refused endoscopy. Compared with the total population, middle-aged men and women were slightly overrepresented among those who had endoscopy. Women who did not respond to the questionnaire or who refused endoscopy were significantly younger compared with the total population.

Figures 1 and 2 present the sex and age-specific frequencies of various endoscopic and histological diagnoses and the proportion of subjects with normal mucosa in their biopsy specimens for 339 men and 280 women. The data for subjects with dyspepsia and endoscopy controls were pooled as the age and sex distribution of the various diagnoses were generally equal in both groups. The age-adjusted frequencies of oesophagitis found on endoscopy were 13.3% in men and 8.4% in women (p = 0.002), and the corresponding figures for duodenitis were 22.8% and 5.9% (p = 0.0001) and for peptic ulcer disease were 5.1% and 7.9% (p = 0.03). The frequencies of various types of gastritis found on histological examination in both sexes and duodenitis in women showed a significant age trend but no significant sex differences (fig 2). No significant differences in age trends between sexes were found for any of the diagnoses.

Table I gives the paired analysis of the prevalences of various endoscopic and histological diagnoses in 273 subjects with dyspepsia and 273 sex and age-matched controls in Stavanger, Norway, in 1987.
TABLE 1: Age and sex adjusted prevalences of endoscopic and histological findings in subjects with dyspepsia and controls. Figures are in parentheses (age adjusted 95% confidence interval).

<table>
<thead>
<tr>
<th>Subjects with dyspepsia</th>
<th>Endoscopic diagnosis</th>
<th>Histological diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epigastric pain (n = 64)</td>
<td>10 (15.1%) (8 to 20.9%)</td>
<td>15 (23.1%) (16.3 to 24.7%)</td>
</tr>
<tr>
<td>Heartburn (n = 142)</td>
<td>3 (2.1%) (1 to 4.2%)</td>
<td>9 (6.3%) (4.5 to 8.5%)</td>
</tr>
<tr>
<td>Both epigastric pain and heartburn (n = 64)</td>
<td>7 (11.1%) (5.4 to 17.7%)</td>
<td>12 (8.5%) (6.3 to 11.7%)</td>
</tr>
<tr>
<td>Controls (n = 310)</td>
<td>25 (8.1%) (5.5 to 12.7%)</td>
<td>12 (3.9%) (2.6 to 6.4%)</td>
</tr>
</tbody>
</table>

Diagnoses based on endoscopic and histological findings in the 723 matched pairs of subjects. The only highly significant differences between subjects with dyspepsia and controls were found in subjects with duodenitis on the basis of endoscopy (p=0.0005) and those with histological findings of chronic atrophic gastritis (p=0.007). When subjects with active chronic gastritis were excluded from the analysis, the difference between subjects with dyspepsia and controls with respect to histological findings indicating chronic gastritis became insignificant. In fact, 90% of controls had atrophic gastritis. More controls than subjects with dyspepsia had duodenitis on histological examination. The figures for duodenitis in grade II (increased cellularity of the lamina propria and abnormality of the surface epithelium) were 20-1% in subjects with dyspepsia and 53-4% in controls.

Of the 129 subjects with dyspepsia, 125 (40.5%) reported having epigastric pain, of whom 64 (51.2%) reported having no simultaneous heartburn, and 245 (79.3%) reported having heartburn or acid regurgitation. Forty-two (17%) of those with heartburn or acid regurgitation had abdominal pain that was not in the epigastric region, 142 (58.0%) had heartburn without abdominal pain, and 61 (24.9%) had both heartburn and epigastric pain.

Table II gives the age and sex adjusted prevalences of the endoscopic and histological findings; there were groupings according to reported symptom. (The 12 subjects with abdominal pain other than epigastric pain were omitted from this analysis.) All diagnoses based on endoscopy showed the highest point estimate among those with both epigastric pain and heartburn, except for oesophagitis, which was at its highest prevalence in the subjects with epigastric pain. The prevalences of peptic ulcer disease and duodenitis were higher among those with heartburn than among those with only abdominal pain, though the confidence intervals overlapped. The prevalences of all gastroduodenal inflammation and peptic ulcer disease were diagnosed on histological examination were, naturally, highest in the group with epigastric pain. The confidence intervals were, however, wide in all three symptom groups, showing the low power of statistical significance due to small numbers.

Discussion

This study was based on a population survey with a high rate of response (88.9%) and was designed to explore the associations between dyspeptic symptoms and endoscopic findings by comparing the findings in subjects with dyspepsia and those in matched controls. To minimise observer bias both the endoscopist and the pathologist were unaware whether or not the subjects had symptoms of dyspepsia, and the pathologist had no information on the endoscopic findings.

Our main observation was that 30% to 50% of the cases of gastroduodenal inflammation and peptic ulcer disease were diagnosed among control subjects and that only 10% of controls were without any endoscopic or histological diagnoses. The considerable overlap in endoscopic and histological findings of the inflammatory process between subjects with and without dyspepsia was unexpected, since the study design was a case-control study. Therefore, it is reasonable to conclude that peptic ulcer disease is a common cause of dyspepsia.

Multiple methodological problems are inherent in this kind of study. In the study, special care should be given to selecting the population to be examined. Compared with subjects in a population-based survey of hospital patients, the selected population regarding age, sex, and severity of symptoms, was different. Furthermore, the expected frequency of endoscopic findings could depend on the type of study, on which dyspeptic symptoms the selection of the population is based. For comparative purposes the wide definition of dyspepsia seems unsuitable.

ASSOCIATION BETWEEN DYSPEPSIA AND DIARRHEA

The association between dyspepsia and peptic ulcer disease is well documented and accepted, although peptic ulcers that do not cause dyspepsia are prevalent. The endoscopic examination, which displays the same clinical picture as peptic ulcer disease, is often associated with dyspepsia, either as a part of the remission of peptic ulcer disease or as a clinical entity on its own. Although the associations between dyspepsia and peptic ulcer disease and dyspepsia and endoscopic duodenitis were confirmed in the present study, 3% of the subjects with these diagnoses did not have dyspepsia.

The association between chronic gastritis and dyspeptic symptoms, on the other hand, is disputed by many authors, though others claim that chronic gastritis can cause symptoms. We found that active chronic gastritis was significantly commoner among subjects with dyspepsia, but gastritis was diagnosed in more than 50% of the controls, and more than 40% of the controls had gastritis with or without symptoms, were diagnosed among people without dyspepsia. Neither grade I nor grade II histologically classified duodenitis was associated with dyspepsia. In fact, the point estimate for duodenitis was higher among controls than among people with dyspepsia.

NON-DISEASE IN UPPER GASTROINTESTINAL TRACT

Endoscopic examination of subjects with dyspepsia supplemented with histological diagnosis, has shown that few subjects (12-25%) have a "normal" upper gastrointestinal tract. Two of the studies were, however, concerned only with gastroduodenal ulcers, in our study the subjects with normal findings were surprisingly few. Some of the endoscopic diagnoses, such as gastritis, duodenal reflex, and hiatus hernia, may be considered non-pathological conditions and be classified as normal. Still, the frequency of these conditions in the general population is unknown.

The prevalence of gastroduodenal inflammation and peptic ulcer disease was higher among controls than among subjects with dyspepsia. These findings suggest that endoscopic examination of subjects with dyspepsia may help to find underlying conditions that are not visible on clinical examination.
The frequency of abnormalities on histological examination would mean that few subjects had a normal mucosa.

The clinical value of pathological findings depends on their ability to classify subjects with common features—for example, having symptoms—or to give information on prognosis. The endoscopic findings in our study, with the possible exceptions of peptic ulcer disease and endoscopic duodenitis, showed no association with dyspeptic symptoms that was of clinical value. This corresponds well with the results of therapeutic trials that show a beneficial effect both on symptoms and peptic ulcer disease and endoscopic duodenitis, whereas convincing evidence of a therapeutic effect on other mucosal inflammations is lacking. In the population the degree of mucosal inflammation apparently represents various degrees in an inflammatory process rather than specific diagnostic entities. Traditionally, clinicians have used as a cut-off point between no disease and disease the presence of an ulcer in the mucosa. The ulceration process must, however, have an initial stage at which the ulcer is invisible through the endoscope. The location, distribution, and severity of the inflammation might contribute when considering alternative cut-off points. In the paired analysis we found no association between symptoms and isolated inflammation in the corpus, antrum, proximal, or distal duodenum. Location and distribution of the inflammation therefore had poor discriminatory power in this study. Although Toukan et al have shown that a high neutrophilic cell count could discriminate between symptom causing gastritis and inflammation not causing dyspepsia, we think that the only rational basis for therapeutic considerations is the symptom, and not endoscopically or histologically diagnosed inflammation of a mild to moderate degree.

The surprising high frequency of positive diagnoses in our study cannot be explained by use of odd provincial diagnostic criteria: both endoscopic and histological examination were performed according to internationally accepted and validated standards of widespread use. When, despite this, the proportion of normal findings on standard endoscopic amounts to a modest 10% it reflects the use of a non-routine concept of normality, where the norm is the non-prevalent, non-inflamed gastrointestinal mucosa. Our findings challenge both endoscopists and pathologists to search for new distinctions between disease and no-disease.

PAPER IV
Erosive Prepyloric Changes in Dyspepsics and Non-Dyspeptics in a Defined Population

The Sørreisa Gastrointestinal Disorder Study

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Institute of Community Medicine, University of Tromsø, and Laboratory of Gastroenterology, Dept. of Medicine, University Hospital, Tromsø, Norway


In this population-based endoscopic survey we found erosive prepyloric changes (EPC) in 38.5% of dyspepsics and 35.1% of non-dyspeptics. EPC were observed more frequently in men than women in both groups. Occurrence of *Helicobacter pylori* was not associated with EPC. No common gastrointestinal symptoms were found to be associated with EPC. Endoscopic duodenitis of the duodenal bulb was found more frequently in subjects with EPC of the two highest grades than in subjects without EPC. Only the highest grade of EPC was associated with chronic gastritis. EPC were associated with cigarette smoking and, among women, also use of alcohol. We conclude that EPC constitute an endoscopic finding without relation to specific symptoms. These changes therefore do not represent a clinical entity, and it is doubtful whether this finding will give the clinician a better understanding of dyspepsia.

Key words: Erosive prepyloric changes; gastric mucosal erosions; gastritis; *Helicobacter pylori*; non-ulcer dyspepsia

Bjørn Berensen, M.D., Institute of Community Medicine, Bredjua, N-9000 Tromsø, Norway

Nesland & Berstad in 1985 (1) described an endoscopic diagnosis based on the presence of standing mucosal folds in the prepyloric region of the stomach (grade 1), sometimes with visible red spots and streaks (grade 2), and in the fully developed picture, called erosive prepyloric changes (EPC), erosions were also present (grade 3). The view that EPC constitute an independent clinical entity was supported in later studies, and EPC were suggested to have an acid-related pathogenesis (2). One author suggested EPC to be related to weakening of the mucosal defence with a defective mucus and bicarbonate barrier (3), whereas others have found EPC associated neither with *Helicobacter pylori* colonization nor with acute inflammation of the stomach mucosa (4).

EPC of grades 2 and 3 were found in 32% of patients with non-ulcer dyspepsia and in 18% of asymptomatic controls (1). This diagnostic entity was believed not to be connected with peptic ulcer disease (1). In another publication, however, the same authors showed reduced epigastric pain and degree of EPC on cimetidine therapy (5), whereas low-dose antacids and pirenzepine did not influence symptoms or the endoscopic picture (6).

The aim of this paper was to describe the occurrence of EPC in dyspeptics and non-dyspeptics in a general population. We also report on the relation between EPC and endoscopic and histologic findings and the associations between EPC and symptoms and possible predisposing factors, including *H. pylori*.

MATERIALS AND METHODS

From March to May 1987 all 2027 men and women, aged 20 to 69 years, of the municipality of Sørreisa in Northern Norway received a postal questionnaire with 119 questions on abdominal complaints, health, lifestyle, diet, and social conditions.

Subjects with confirmatory answers to the first two or the last of the following questions were classified as dyspeptics: ‘Have you ever had abdominal pain of at least 2 weeks' duration?’, and ‘If yes, was the pain located to the upper abdomen?’. and ‘Have you ever had heartburn or acid regurgitation almost daily during at least 1 week?’

Of the 2027 persons invited, 88.9% returned the questionnaire. Dyspeptics without a history of peptic ulcer, gallstones, kidney stone, cardiac diseases, or abdominal surgery were offered an endoscopy. Corresponding non-dyspeptic controls matched for sex and age, within the same 10-year age groups, were randomly selected and offered an endoscopy as well. Non-dyspeptics refusing endoscopy were replaced in a second, similar procedure. Of 782 subjects invited to endoscopy, 619 men and women (79.2%) were endoscopical, of which 309 were dyspeptics and 310 non-dyspeptics. All were endoscoped within 1 month after returning their questionnaires. A detailed description of the methods is published elsewhere (7).

The study was approved by the regional committee of medical research ethics.
Table I. The age- and sex-specific percentages of erosive prepyloric changes (grades 1–3) in 309 dyspeptic and 310 non-dyspeptics, Sarre 1987

<table>
<thead>
<tr>
<th>Age group, years</th>
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<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dyspeptics</td>
<td></td>
<td>Non-dyspeptics</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Total</td>
<td>Men</td>
<td>Women</td>
<td>Total</td>
<td></td>
</tr>
<tr>
<td>20-29</td>
<td>35</td>
<td>30</td>
<td>65</td>
<td>36</td>
<td>23</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>30-39</td>
<td>44</td>
<td>42</td>
<td>86</td>
<td>46</td>
<td>42</td>
<td>88</td>
<td></td>
</tr>
<tr>
<td>40-49</td>
<td>54</td>
<td>34</td>
<td>88</td>
<td>53</td>
<td>37</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>50-59</td>
<td>24</td>
<td>22</td>
<td>46</td>
<td>23</td>
<td>22</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>12</td>
<td>12</td>
<td>24</td>
<td>12</td>
<td>16</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>169</td>
<td>140</td>
<td>309</td>
<td>170</td>
<td>140</td>
<td>310</td>
<td></td>
</tr>
</tbody>
</table>

Endoscopy

All endoscopies were performed by one of the authors (B. Bernersen), who is a trained endoscopist. The endoscopist was ‘blinded’ in the sense of not knowing whether he examined a dyspeptic or a non-dyspeptic. Subjects were offered intravenous premedication with 5 mg of a commercially available diazepam preparation (Diaminal®, KabiVitrum AB, Stockholm, Sweden). Atropine was not given as premedication. Biopsy specimens for histologic examination were taken from the proximal and distal parts of the duodenum, from both the greater and the lesser curves of the antrum and corpus of the stomach and also from the lesions. Biopsy specimens for culture of *H. pylori* were taken from the lesser and from the greater curve of the antrum approximately 3 cm proximal to the pyloric ring. Erosive prepyloric changes were noted and classified after air inflation of the stomach and before conducting the endoscope into the duodenum in accordance with the description by Nesland & Berstad (1).

*Helicobacter pylori*

Biopsy specimens for culture were placed in 0.5 ml of a glucose/saline solution (25% glucose in 0.9% saline solution), ground, and placed on one blood agar plate and one plate of brain-heart infusion agar with horseblood within 5 min after endoscopy. The plates were incubated in a Gas Pack jar at 37°C under anaerobic conditions (Gas generating box Campylobacter bioMerieux). After 3–10 days the positive cultures of grey, translucent colonies were tested for urease, catalase, and oxidase activity. They were also Gram-stained for microscopic examination. The diagnosis of *H. pylori* was made when the enzyme reactions mentioned above were positive together with a typical Gram stain.

Histologic examination

The specimens were formalin-fixed and prepared in accordance with standard methods. Haematoxylin/cosin- and periodic acid-Schiff/Aleian blue-stained sections were interpreted at the Dept. of Histopathology at the University Hospital of Tromsø by one experienced pathologist, without any clinical or microbiologic information available. Inflammation in the gastric and duodenal mucosa was classified in accordance with Whitehead et al. (8) and, when active, inflammation was present, in accordance with Owen (9).

Regression analysis

The following independent variables were explored and finally assessed in logistic regression: age; sex; daily smoking (yes/no); number of cigarettes smoked daily; coffee consumption (none or less than 1 cup a day, 1–5 cups, and 6 or more a day); beer, wine, and liquor consumption (grade 0–2); nutrition as baby (mother’s milk or not); regularity of meals; excessive use of spices, ketchups, or mustard; use of aspirin; use of non-steroidal antiinflammatory drugs; sleep; pills and ataraxics; and shift work (all yes/no); social status (4 grades); and physical activity (graded 1–4: sedentary mode-rate, active, and hard training). Only the following variables contributed significantly to the final model: sex; daily smoking; and beer, wine, and liquor consumption.

The following symptoms were also explored in a separate analysis similar to the procedure mentioned above: various combinations of irritative bowel symptoms (in which a combination of abdominal pain in the lower part of the abdomen, relief of pain with bowel movement, loose or frequent stools or very hard stools, and presence of much stools were used); frequent upper abdominal pain or heartburn; abdominal pain for the last 2 weeks; abdominal pain of long duration; frequent globus sensation; nausea; haematemesis; blood with stools; melaena (all yes/no); and nervous symptoms (graded 1–3 in accordance with frequency of combinations of frequent headache, unpecific vertigo, palpitations, and insomnia). None of these variables showed significance at any step of the analysis.

Statistical methods

Chi-square statistics were used to compare EPC in groups. Age trends were tested with the Mantel–Haenszel chi-square test. Logistic regression and adjustment for age and sex distribution by analysis of covariance were made in the SPSSX statistical program. We analysed our data both 273 complete pairs and in groups. As the analyses gave
Table II. Percentage distribution and mean age in graded erosive prepyloric changes (EPC) in 309 dyspeptics and 310 non-dyspeptics aged 20-69 years, Sarriera, 1987

<table>
<thead>
<tr>
<th>Grade of EPC</th>
<th>Dyspeptics, n = 309</th>
<th>Non-dyspeptics, n = 310</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>No EPC</td>
<td>190</td>
<td>61.5</td>
</tr>
<tr>
<td>Grade 1</td>
<td>70</td>
<td>22.7</td>
</tr>
<tr>
<td>Grade 2</td>
<td>28</td>
<td>9.0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>21</td>
<td>6.8</td>
</tr>
</tbody>
</table>

CI denotes 95% confidence interval.

Table III. The age- and sex-adjusted percentages of endoscopic findings in accordance with grading of erosive prepyloric changes (EPC) in 619 subjects aged 20-69 years, Sarriera, 1987

<table>
<thead>
<tr>
<th>Endoscopic findings</th>
<th>No EPC, n = 391</th>
<th>EPC grade 1, n = 139</th>
<th>EPC grade 2, n = 55</th>
<th>EPC grade 3, n = 34</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>CI</td>
<td>%</td>
<td>CI</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>9.9</td>
<td>(7.3-13.5)</td>
<td>10.2</td>
<td>(5.6-16.3)</td>
</tr>
<tr>
<td>Bile reflux</td>
<td>15.5</td>
<td>(12.1-19.5)</td>
<td>13.3</td>
<td>(8.1-20.5)</td>
</tr>
<tr>
<td>Duodenitis of the duodenal bulb</td>
<td>11.5</td>
<td>(8.6-15.3)</td>
<td>9.4</td>
<td>(5.0-15.4)</td>
</tr>
<tr>
<td>Deformity of the duodenal bulb</td>
<td>4.5</td>
<td>(2.8-7.1)</td>
<td>3.2</td>
<td>(1.5-7.7)</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>1.3</td>
<td>(0.4-3.0)</td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>1.5</td>
<td>(0.6-3.4)</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

CI denotes confidence interval.

same results, we have chosen to present results only from the total material.

RESULTS

EPC were found in 119 (38.5%) of the dyspeptics and 109 (35.1%) of the non-dyspeptics, a non-significant difference (p = 0.40). Table I shows the age and sex distribution of all grades of EPC together. EPC were observed more frequently in men than in women, both among dyspeptics and non-dyspeptics (p = 0.0004). The male to female ratio was 1.36 in dyspeptics and 1.8 in non-dyspeptics. Table II shows the mean age of those without EPC and of the subjects with the various grades of EPC. Non-dyspeptic subjects with EPC grade 3 had a slightly but significantly higher mean age than those with EPC grade 1 and those without EPC. There was no age trend within any of the gradings of EPC.

Table III shows the relations between EPC and endoscopic findings. EPC of grades 2 and 3 were associated with duodenitis of the duodenal bulb (p < 10^-6), and EPC of grade 3 had deformity of the duodenal bulb more frequently than those without EPC (p = 0.036). There were no such differences for the other endoscopic features listed.

Table IV shows the relation of EPC to histologic diagnoses and positive culture of H. pylori. There was no association between histologic gastritis and EPC. An analysis with the subtypes of gastritis showed more chronic atrophic gastritis (p = 0.012) and slightly more subacute gastritis (p = 0.032) in subjects with EPC grade 3 than in those without EPC. The frequency of H. pylori-positive cultures in EPC was the same as in subjects without EPC (p = 0.19).

An analysis of common gastrointestinal symptoms showed no significant association of any symptom or symptom complex with EPC. The logistic regression analysis of possible risk factors for EPC (Table V) showed that men were more likely to have EPC than women. This finding was consistent even after adjustment for smoking, consumption of alcoholic beverages, and occurrence of endoscopic duodenitis in an analysis of covariance. Smoking was positively associated with EPC. Moreover, EPC of grades 2 and 3 were positively associated with use of alcoholic beverages. In a sex-specific analysis the association of EPC with the degree of alcohol consumption was inconsistent with a significant association only in women. EPC were not associated with the reported use of aspirin or non-steroidal antiinflammatory drugs.

DISCUSSION

This study demonstrated that endoscopic findings described as erosive prepyloric changes are frequent in a general...
population. In our study dyspeptic subjects did not have EPC more frequently than non-dyspeptics. Moreover, the analyses did not reveal any specific symptoms that could increase the likelihood of making these endoscopic findings. On this point our study did not support the conclusion based on findings in a patient population and in asymptomatic volunteers, which suggested that the recognition of EPC may lead to a more accurate definition of a group with ulcer-like symptoms (1). It is more likely that studies using patients will be biased.

There is, however, a striking difference between sexes in that men are more likely to have EPC. This is a new finding, as patient populations showed a male to female ratio in EPC of 1.1 (1) and in gastric erosions of 0.98 (10). This difference was consistent after adjustment for sex differences in smoking, use of alcoholic beverages, and frequency of endoscopic duodenitis.

The analysis of possible risk factors in this study made it likely that various substances that usually may be regarded as noxious to the gastric mucosa might have some impact. Strangely, we found no association between EPC and the use of aspirin or non-steroidal anti-inflammatory drugs, but this may be due to a lack of coincidence in point of time for intake of the drugs and the time of endoscopy. Our question to the participants was, however: 'Do you often take one or more of the following drugs listed: Aspirin etc?'. Our study may show a possible noxious effect of cigarette smoking and alcohol. It is also possible that these substances, as mentioned, may act as stimulants of gastric secretion. Nesland & Berstad (1) found the same maximum acid output (MAO) in patients with EPC as in controls and lower MAO than in duodenal ulcer patients. Study of EPC in patients showed, however, a significant improvement measured by the grading scale of EPC in patients with EPC grades 2 and 3 treated for 4 weeks with cimetidine (5), which may lead us to suspect an association between EPC and acid secretion. In our study we have no data on this aspect, as acid secretion was not studied. Our study showed, however, a relation between EPC and endoscopic duodenitis of the duodenal bulb, which may suggest high gastric acid secretion (11).

The histologic picture in EPC is that of chronic gastritis. We studied multiple biopsy specimens taken in a standardized pattern in our material, but not specimens especially designed to reveal erosions. We may therefore have missed some features of acute inflammation described in connection with erosions, as found by others (12).

*H. pylori* was not related to EPC to any extent except that of chronic gastritis, in agreement with an earlier publication (4). For EPC grade 3 the number may be too small to show an association with *H. pylori* despite the sharp association with subacute and chronic gastritis.

EPC are an endoscopic finding without relation to specific symptoms in our study. They therefore do not represent a clinical entity and are most unlikely to lead us to a better understanding of dyspepsia. The endoscopic feature may be acid-related, although the information is controversial. It may be precipitated through cigarette smoking and possibly...
REFERENCES


Received 27 August 1991
Accepted 22 October 1991
PAPER V
Is *Helicobacter pylori* the cause of dyspepsia?

Bjørn Bernersen, Roar Johnsen, Leif Bostad, Bjørn Straume, Ann-Inger Sommer, Per G Burhol

**Abstract**

**Objective**—To determine the association between infection with *Helicobacter pylori* and dyspepsia. **Design**—Cross sectional study of dyspeptic subjects and age and sex matched controls identified by a questionnaire survey of all inhabitants aged 20-69. (Endoscopy, histological examination, and microbiological examinations of biopsy samples from the gastric mucosa were performed blind.) **Setting**—Population based survey in Sørreisa, Norway. **Subjects**—All 782 dyspeptic subjects (excluding those with a previous history of peptic ulcer, gall stones or kidney stones, and coronary heart disease) and controls were offered an endoscopy, of whom 399 dyspeptic subjects and 310 controls attended. **Main outcome measures**—Prevalences of endoscopic and histological diagnoses and of cultures positive for *H pylori*. **Results**—A high prevalence of positive cultures, increasing with age, was found in both dyspeptic subjects (48%) and non-dyspeptic controls (36%) (p<0.004). Positive cultures in both dyspeptic subjects and controls were strongly associated with histological gastritis (70%, 95% confidence interval 65.5-75.5; 50%, 90% confidence interval 39-66; respectively) and peptic ulcer (92%, 95% confidence interval 92-94; 64%, 90% confidence interval 54-76, respectively). Only 3% of subjects with a histologically non-inflamed gastric mucosa had this infection (dyspeptic subjects 2%, 0-2 to 4%; controls 4%; 1.2 to 8.). **Conclusions**—The relation between dyspeptic symptoms and *H pylori* is dubious; *H pylori* seems to have a pathogenetic role in gastritis and may be a contributing factor but not a cause of peptic ulcer.

Introduction

Dyspepsia requires costly management despite lack of knowledge of its causes. The rediscovery by Warren and Marshall of *H pylori* in the gastric mucosa which were related to gastritis and the study of its prevalence in healthy, normal populations and of the concurrence of *H pylori* infection and symptoms of dyspepsia. Only one study on the occurrence of *H pylori* in a general population has been published. Population based data are mandatory in considering *H pylori* as a pathogenic agent in gastritis and peptic ulcer disease and as a possible cause of dyspepsia.

As part of a population based study we examined endoscopy unscreened subjects with dyspepsia and age and sex matched controls to determine the prevalence of *H pylori* infection and its relation to endoscopic and histological diagnoses.

Subjects and methods

From March to May 1987 all inhabitants of the municipality of Sørreisa in northern Norway aged 20-69 years, 2027 men and women, received a postal questionnaire with 119 questions about abdominal complaints, health, lifestyle, diet, and social conditions. All of the subjects answering positively to the last two questions: "Have you ever had abdominal pain lasting at least two weeks' duration?" and "If yes, was the pain located to the upper abdomen?" or the last question: "Have you ever had heartburn or acid regurgitation almost daily during at least one week?" were considered to have dyspepsia.

After exclusion of 89 dyspeptic subjects with prior history of peptic ulcer, 15 with gall stones or kidney stones, and 33 with coronary heart disease, the remaining subjects were offered an endoscopy free of charge. Corresponding healthy, non-dyspeptic controls were matched for sex and age within the same 10 year age group were randomly selected and offered an endoscopy. The controls reported that they had no history of dyspepsia and had not consulted their general practitioner for dyspepsia. Of 782 subjects invited to endoscopy, 619 (79.9%) (309 dyspeptic subjects and 310 non-dyspeptic controls) had an endoscopy, all within one month after returning their questionnaires. A detailed description of the methods has been published elsewhere. The study was approved by the regional committee for medical research ethics.

ENDOSCOPY

All endoscopies were performed by BB, who is a trained endoscopist. He was "blinded" in the sense not knowing whether he was examining a dyspeptic or a non-dyspeptic subject. Endoscopic findings were classified according to criteria described by Savary and Miller (esophagitis), Johnson and Dickson (cardia), Myren and Strck-Hanssen (endoscopic gastric mucosal appearance), and Neslund and Berstad (gastrroduodenal reflex).
prepyloric changes,\textsuperscript{15} Venables (duodenitis),\textsuperscript{12} and Bernerse et al. (peptic ulcer and deformed duodenal bulb).\textsuperscript{17}

Biopsy specimens for histological examination were taken from the proximal and distal parts of the duodenum, from both the greater and lesser curvatures of the corpus and antrum of the stomach, and from all lesions as well. Biopsy specimens for culture were also taken from the lesser and from the greater curvature of the antrum about 3 cm proximal to the pyloric ring. The endoscopes (Olympus gastroscope type GIF-Q 20) and biopsy forceps were cleaned and thereafter disinfected in a commercially available glutaraldehyde solution (Korsol, Norforma, Rud, Norway) between each endoscopy.

MICROBIOLOGICAL EXAMINATION

Biopsy specimens for culture were placed in 0.5 ml of glucose-saline solution (25% glucose in 0.9% saline solution), ground, and cultured on blood agar and on brain-heart infusion agar containing horse (5% v/v) blood within five minutes after endoscopy. The media were incubated in a Gas Pack jar at 37°C under microaerobic conditions (Gas generating box Campylobacter bioMérieux). After three to 10 days any positive cultures, appearing as grey translucent colonies were used for urease, catalase, and oxidase activities. They were also Gram stained for microscopic examination. The number of positive colonies was evaluated using a semiquantitative scale. \textit{H. pylori} was identified on the basis of positive urease, catalase and oxidase reactions together with a typical microscopic appearance on Gram staining. There were no problems with contamination. The microbiohistologist had no clinical information on the subjects involved.

### TABLE I

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dyspeptic subjects (n=309)</th>
<th>Controls (n=110)</th>
<th>Total (n=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%) positive</td>
<td>No (%) positive</td>
<td>No (%) positive</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Dyspeptic subjects</td>
<td>2 (2.2) to 7.0</td>
<td>2 (1.8) to 6.0</td>
<td>4.9 (2.2 to 7.0)</td>
</tr>
<tr>
<td></td>
<td>167 (54.5)</td>
<td>112 (54.6)</td>
<td>279 (54.5)</td>
</tr>
<tr>
<td>Controls</td>
<td>3 (2.7) to 6.0</td>
<td>1 (0.9) to 6.0</td>
<td>4.0 (2.7 to 6.0)</td>
</tr>
<tr>
<td></td>
<td>75 (68.2)</td>
<td>61 (55.5)</td>
<td>136 (68.2)</td>
</tr>
</tbody>
</table>

### TABLE II

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Dyspeptic subjects (n=309)</th>
<th>Controls (n=110)</th>
<th>Total (n=419)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No (%) positive</td>
<td>No (%) positive</td>
<td>No (%) positive</td>
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<td></td>
<td>2 (2.2) to 7.0</td>
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<td>4.9 (2.2 to 7.0)</td>
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<td>3 (2.7) to 6.0</td>
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</tr>
<tr>
<td></td>
<td>75 (68.2)</td>
<td>61 (55.5)</td>
<td>136 (68.2)</td>
</tr>
</tbody>
</table>

### RESULTS

\textit{H. pylori} was cultured from 259 (41.8%) of the participating subjects (table I). Significantly more positive cultures were obtained from dyspeptic subjects than from non-dyspeptic controls (48.8% vs. 36.8%, p=0.004). The odds ratios were 1.85 (95% confidence interval 1.16 to 2.95) for men and 1.37 (95% confidence interval 1.02 to 2.16) for women and were only marginally different (p=0.03). There was a linear increasing trend of prevalence of \textit{H. pylori} in age (p=0.036) and controls (p=0.003), which persisted when sex was controlled for.

The prevalence of \textit{H. pylori} in the endoscopic diagnostic subgroups, both with and without peptic ulcer, was compared with that in the group with normal endoscopic findings, controlling for age, sex, and dyspeptic symptoms (table I). Only in the peptic ulcer group was it higher than in the group with normal endoscopic diagnosis (p=0.035).

Positive culture of \textit{H. pylori} was strongly related to histological findings in the gastric mucosa (table II). The prevalence of \textit{H. pylori} was rare (3%) in the subjects with a histologically normal gastric mucosa. When histological gastritis was divided into subtype groups according to the degree of inflammation, there were only insignificant differences among positive culture rates for the respective subtypes. When histological gastritis of the corpus and antrum were studied separately, however, the prevalence of \textit{H. pylori} infection was significantly higher when the chronic active gastritis.
Discussion

The strength of this study is its population base and its design to avoid observer bias. Clinical information was not available to the endoscopist, pathologist, or microbiologist. Dyspepsia has no generally accepted definition, and endoscopic and histologic findings may vary with different intensity and duration of the dyspeptic symptoms. We chose to restrict the definition to the most commonly accepted symptoms. We found a high prevalence of *H. pylori* in both the dyspeptic subjects and non-dyspeptic controls but a strong association between *H. pylori* and peptic ulcer and histologic gastritis. Subjects with a histologically normal mucosa had an almost negligible prevalence of *H. pylori*. The rate of positive cultures of *H. pylori* in this group is within the range of error for histologic findings. It seems reasonable to believe that a histologically normal gastric mucosa is incompatible with *H. pylori* infection.

Other authors have used different methods for the detection of the organism in stomach tissue samples, in culture, or by other means, and occasionally by using various staining techniques to detect the organism in criteria for the presence of *H. pylori* infection. Discrepancies exist between results based on different diagnostic procedures. We used only isolation of *H. pylori* as a criterion, and thus we may have detected somewhat lower prevalences than if we had used all criteria for the presence of *H. pylori* in the gastric mucosa. On the other hand, a rather low occurrence of *H. pylori* in subjects with a histologically normal mucosa indicates a high specificity. This finding agrees with results in the Finnish population based on similar criteria of normality, in which *H. pylori* was present in 5% of the subjects with a normal antro mucosa.

The prevalences in non-dyspeptic controls in our study were within the same range as in previous studies, showing that *H. pylori* infection is quite common even among subjects without dyspepsia, whereas the prevalence of *H. pylori* infection in dyspeptic controls was lower than previously reported from patient populations. This may partly reflect our exclusion of subjects with a previously diagnosed peptic ulcer.

Even though there was a higher prevalence of *H. pylori* infection in dyspeptic than non-dyspeptic subjects, 43% of positive cultures were found among non-dyspeptic controls. Some authors have suggested that this organism plays a major part in non-ulcer dyspepsia. The high prevalence in non-dyspeptic controls indicates that *H. pylori* infection alone is unlikely to provoke dyspeptic symptoms.

Our study confirms the association between gastritis and *H. pylori* infection. The interesting point is why *H. pylori* is absent in a third of subjects with histologic gastritis. One may suggest other properties of the mucosa in these subjects, but a clinical course in which the inflammatory process proceeds after the disappearance of *H. pylori* may also be proposed.

Peptic ulcer was the only endoscopic finding associated with a significantly higher frequency of *H. pylori* infection than endoscopically normal mucosa. Peptic ulcer is associated with gastritis. Antral gastritis is found in a high proportion of patients with duodenal ulcer, and gastric ulcers are usually found in an area with chronic gastritis. As *H. pylori* infection in our study was strongly associated with gastritis, our finding of a prevalence of *H. pylori* infection in peptic ulcer as high as 86.5% may support the theory of a pathogenetic role for this organism in peptic ulcer disease. *H. pylori* infection and gastritis were, however, found in a much higher proportion of controls.

References


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10. APPENDIX
Fordøyelsesbesvær eller magesårlignende plager er svært vanlig. Bare et fåttall av de som har magesårlignende plager har imidlertid magesår. Vi vet ikke hvor mange som har slike plager i en vanlig befolkning. Heller ikke vet vi årsaken til slike plager, eller om personer med slike plager vil utvikle magesår senere.

Det vil derfor være av stor betydning for forståelsen og dermed behandlingen av slike plager å kunne gjennomføre en undersøkelse over fordøyelsesbesvær eller magesår-lignende plager i Sørreisa. Denne undersøkelsen er et samarbeidsprosjekt mellom Kommunehelsetjenesten i Sørreisa, Gastroenterologisk seksjon, Medisinsk avdeling, Regionsykehuset i Tromsø og institutt for samfunnsmedisin, Universitetet i Tromsø.

Som det vil fremgå av vedlagte spørreskjema, ønsker vi å kartlegge følgende som kan være av betydning:

- Generelle forhold.
- Magaplager og beslektede forhold.
- Andre plager.
- Slektforhold med tanke på mulig arvelighet.
- Spisevaner som kan virke utløsende og forverrende.
- Likeså forbruk av kaffe, te, tobakk, alkohol og medikamenter.
- yrkesmessige og sosiale forhold.

De fleste som har eller har hatt fordøyelsesbesvær vil senere få tilbud om en nærmere undersøkelse av magen på kommunlegekontoret i Sørreisa ved overlege Bjørn Bernersen. Det er viktig at så mange som mulig møter opp til denne undersøkelsen.

Vi håper at alle som får tilsendt dette spørreskjemaet tar brytet med å fylle det ut og å returnere det så fort som mulig. All deltagelse er frivillig.

Innsendte spørreskjemaer vil bli gjennomgått av medisinsk personell og behandlet strengt konfidensielt på samme måte som legejournaler. Alle opplysninger blir lagret på EDB og gjort utilgjengelig for uvedkommende.

Vennlig hilsen

Per A. Stakkevold
kommunelege I

Bjørn Bernersen
overlege

Idar Elvemo
kommunelege II
Magesmerter

7. Har du noen gang hatt smerter eller «verken» i magen som har vart i minst to uker?  
   JA □ 007.1  
   NEI □ 007.2  
   (Omgangssynke (<rekkeiske>) regnes ikke med)  
   Hvis «NEI», gå direkte til spørsmål nr. 29.  
   Hvis «JA», fortsett med spørsmål nr. 8.

8. Sitter smertene eller «verken» i  
   □ over del av magen? 008.1  
   □ nedre del av magen? 008.2  
   □ hele magen? 008.3

9. Angi så nøyaktig som mulig hvilket årstall du første gang merket smertene eller «verken» i magen: 009

10. Har smertene eller «verken» i magen noen gang vært tilstede hver dag i mer enn to måneder?  
    (Sett kryss i den ruten som passer)  
    JA □ 010.1  
    NEI □ 010.2

11. Har du hatt smerter eller «verken» i magen de siste to ukene?  
    (Sett kryss i den ruten som passer)  
    JA □ 011.1  
    NEI □ 011.2

12. Er smertene eller «verken» jevnt over tilstede  
    □ i perioder av ukens vanligvis? 012.1  
    □ i perioder av måneders vanligvis? 012.2  
    □ bestandig? 012.3

13. Hvilke måneder er smertene eller «verken» i magen vanligvis verst?  
    □ Januar–februar: 013.1  
    □ Mars–april: 013.2  
    □ Mai–juni: 013.3  
    □ Juli–august: 013.4  
    □ September–oktober: 013.5  
    □ November–desember: 013.6  
    □ Ingen forandringer gjennom året: 013.7

14. Bli smertene eller «verken» i magen vanligvis  
    □ bedre når du spiser? 014.1  
    □ verre når du spiser? 014.2  
    □ påvirket når du spiser? 014.3

15. Bli smertene eller «verken» i magen vanligvis  
    □ bedre ved fysiske anstrengelser? 015.1  
    □ verre ved fysiske anstrengelser? 015.2  
    □ påvirket ved fysiske anstrengelser? 015.3
16. Hender det at du vækker om natten av smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  06.1

17. Har du søkt lege på grunn av smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  01.7

18. Hvis «JA», hvor mange ganger har du søkt lege sist året på grunn av smertene eller «verken» i magen? 
   Antall  01.8

19. Har du vært henvist til, eller innlagt i sykehus på grunn av smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  01.9

   (Skriv navnet her):  
   Hvilket år ble du henvist eller undersøkt sist gang?  02.0

21. Har du vært sykmeldt for smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  02.1

22. Hvis «JA», angi hvor mange uker du har vært sykmeldt for smertene eller «verken» i maonen i løpet av de siste 12 månedene:  02.2

   (Sett kryss i den ruten som passer)  02.3

24. Hvis «JA», har disse midlene hjulpet mot smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  02.4

25. Har du fått andre medikamenter på respekt for smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  02.5

| Hvis «JA», kryss av for den gruppen under spørsmålene 26, 27 og 28, hvor du eventuelt finner navnet på det medikamentet du har fått. Om nødvendig se etter på respekt, medisinlæs, eller pakning om du finner navnet. Svar også på om dette medikamentet har hjulpet eller ikke hjulpet mot smertene eller «verken» i magen. |

26. Cimal, Cimelicid, Gastrobilian, Tagamet, Ranacid eller Zantac? 
   (Sett kryss i den ruten som passer)  02.6

27. Egezil Duretter, Daricon, Gastrozepin, Librax, Oximin, Ulcobian? 
   (Sett kryss i den ruten som passer)  02.7

28. Surmontil? 
   (Sett kryss i den ruten som passer)  02.8

29. Hvis «JA», har dette hjulpet mot smertene eller «verken» i magen? 
   (Sett kryss i den ruten som passer)  02.9

30. Er du ofte plaget av kvalme eller oppkast? 
   (Sett kryss i den ruten som passer)  01.1

31. Har du noen gang kostet opp blod? 
   (Sett kryss i den ruten som passer)  01.2

32. Har du vansker med å svelge, eller følelse av at maten stopper opp i halsen eller kryystet? 
   (Sett kryss i den ruten som passer)  01.3

33. Er du ofte plaget av oppblåsthed, rumling i magen eller rikelig luftutgåv fra endetarmen? 
   (Sett kryss i den ruten som passer)  01.4

34. Hvis «JA», blir oppblåstheden eller rumlingen bedre av avføring eller luftutgåv fra endetarmen? 
   (Sett kryss i den ruten som passer)  01.5

35. Er avføringen din vanligvis: 
   Normal? 
   Los? 
   Hard og parlet? 
   Vokslede los og hard? 

36. Har du i perioder tre eller flere avføring daglig? 
   (Sett kryss i den ruten som passer)  01.6

37. Har du i perioder avføring sjeldere enn hver tredje dag? 
   (Sett kryss i den ruten som passer)  01.7

38. Har du ofte sett slim i avføringen? 
   (Sett kryss i den ruten som passer)  01.8

39. Har du noen gang sett friskt, rost blod i avføringen? 
   (Sett kryss i den ruten som passer)  01.9

40. Har du noen gang hatt bekvemt eller fjærleg eller avføring? 
   (Sett kryss i den ruten som passer)  01.10

41. Hvis «JA», brukte du forut for dette jerntabletter eller jernmikstur? 
   (Sett kryss i den ruten som passer)  01.11

42. Har du noen gang hatt hemmorroider eller sår/rører i endetarmåpeningen? 
   (Sett kryss i den ruten som passer)  01.12

43. Har du eller har du fått påvist magesår? 
   (Sett kryss i den ruten som passer)  01.13

44. Er du operert for magesår? 
   (Sett kryss i den ruten som passer)  01.14

45. Har du eller har du hatt gallestein? 
   (Sett kryss i den ruten som passer)  01.15

46. Har du vært operert for noe annet i magen? 
   (Sett kryss i den ruten som passer)  01.16

47. Hvis du har vært operert i magen, angi da så nøydlig som mulig når du ble operert i magen siste gang 
   Årstall

og angi også ved hvilket sykehus 
(Skriv navnet på sykehuset her):
48. Har du eller har du hatt angina pectoris (hjertekramp) i det siste året? (Sett kryss i den røde området) NEI

49. Har du eller har du hatt hjerteinfarkt (sår på hjertet) i det siste året? (Sett kryss i den røde området) NEI

50. Har du eller har du hatt annen hjertesykel? (Sett kryss i den røde området) NEI

51. Har du sukkersykdom? (Sett kryss i den røde området) NEI

52. Har du eller har du hatt nyrestein? (Sett kryss i den røde området) NEI

53. Har du hatt allergisk reaksjon i øyne/ nese (hayfever, astma)? (Sett kryss i den røde området) NEI

54. Har du hatt allergisk reaksjon i løv eller pollen (astma)? (Sett kryss i den røde området) NEI

55. Har du hatt allergisk reaksjon i hud (utslett), (Sett kryss i den røde området) NEI

56. Har du hatt allergisk reaksjon i mage-gutt? (Sett kryss i den røde området) NEI

57. Har du noen gang reagert allergisk på mat eller drikke? (Sett kryss i den røde området) NEI

58. Har du ofte en eller flere av følgende plager? (Sett kryss i den røde området)
   - Hodepine: .
   - Småbeholder:
   - Hjertet:
   - Søvnsviktet:
   - Menstruasjonsplager:

59. Har du ledig eller ofte ledig- og muskelsmerte? (Sett kryss i den røde området) NEI

60. Plages du av forbindelser eller umunnravn? (Sett kryss i den røde området)
   - Aldri:
   - Selvert:
   - Av og til:
   - Ofte:

61. Hvordan synes du din helsetilstand er nå? (Sett kryss i den røde området)
   - Meget bra:
   - Bra:
   - Middel i balanse:
   - Dødelig:
   - Meget dødelig:

62. Oppgi din øyne høyde og vekst nå:
   - Høyde (i cm): cm
   - Vekt (i kg): kg

63. Angi, så fremt du kan, om du har spesialfôr fôr barn eller ikke: (Sett kryss i den røde området)
   - Brynemilk:
   - Kunstig ernæring (fleske):
   - Begge deler:
   - Vel ikke:

64. Angi hvor mange nålevende sesker du har...

65. Angi hvor mange av dine sesker som er døde...

66. Angi hvor mange barn du har...

67. Har noen av disse i din familie hatt magesår?
   - Ektefelle/samboeren:
   - Mor:
   - Fart:
   - Søster:
   - Bror:
   - Barn:
   - Ingen:

68. Har noen av disse i din familie hatt fordysepsisvaruten å ha hatt magesår?
   - Ektefelle/samboeren:
   - Mor:
   - Fart:
   - Søster:
   - Bror:
   - Barn:
   - Ingen:

69. Spiser du til faste idretter?
   - Alltid:
   - Vanligvis:
   - Av og til:
   - Så godt som aldri:

70. Spiser du vanligvis frokost hver dag? (Sett kryss i den røde området) NEI

71. Spiser du vanligvis middag hver dag? (Sett kryss i den røde området) NEI

72. Spiser du vanligvis etter kl. 10 om kvelden? (Sett kryss i den røde området) NEI

73. Spiser du vanligvis mellom hovedmatmidlene? (Sett kryss i den røde området) NEI

74. Har du for vane å ette maten ekstra? (Sett kryss i den røde området) NEI

75. Har du for vane å bruke mye krydder? (Sett kryss i den røde området) NEI

76. Har du for vane å bruke mye senner? (Sett kryss i den røde området) NEI

77. Har du for vane å bruke mye ketchup? (Sett kryss i den røde området) NEI

78. Hva slags brod spiser du vanligvis?
   - Loff:
   - Fløt (lyst brod):
   - Grovt (merkt brod):
   - Klubbred:
88. Røker du sigaretter daglig (enten ferdige eller rullede)? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 089.1

89. Hvis «JA», røker du mindre enn en for 5 år siden? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 090.1

90. Hvis «NEI», har du rokt sigaretter tidligere? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 091.1

91. Hvis du har rokt sigaretter tidligere; hvor lenge er det siden du sluttet?
   - Mindre enn 3 måneder:
   - Mellom 3 måneder og 1 år:
   - Mellom 1 og 5 år:
   - Mer enn 5 år:
   JA [ ] NEI [ ] 092.1

92. For alle som røker eller som har rokt sigaretter tidligere, angi hvor mange år du tilsammen har rokt sigaretter daglig? (Sett kryss i den ruten som passer)
   Antall år [ ] 093.1

93. Angi hvor mange sigaretter du røker/eller du roker tidligere daglig? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 094.1

94. Røker du daglig annen tobakk som sigarer, sigarillos eller pipetobakk? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 095.1

95. Bruker du vanligvis snus eller skråtobakk daglig? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 096.1

96. Hvis «JA», angi hvor mange røker snus eller skråtobakk du bruker ukentlig: (Sett kryss i den ruten som passer)
   Antall [ ] 097.1

97. Smaker du fra tid til annen alkoholholdige drikker som øl, vin eller brennevin? (Sett kryss i den ruten som passer)
   JA [ ] NEI [ ] 098.1

98. Hvis «JA»:
   - Aldri, eller noen få ganger i året: (Sett kryss i den ruten som passer)
   - 1-2 ganger i måneden:
   - Omtrent 1 gang i uken:
   - 2-3 ganger i uken:
   - Omtrent hver dag:
   JA [ ] NEI [ ] 099.1

99. Hvor ofte pleier du å drikke vin?
   - Aldri, eller noen få ganger i året: (Sett kryss i den ruten som passer)
   - 1-2 ganger i måneden:
   - Omtrent 1 gang i uken:
   - 2-3 ganger i uken:
   - Omtrent hver dag:
   JA [ ] NEI [ ] 100.1

100. Hvor ofte pleier du å drikke bronnavin?
    - Aldri, eller noen få ganger i året: (Sett kryss i den ruten som passer)
    - 1-2 ganger i måneden:
    - Omtrent 1 gang i uken:
    - 2-3 ganger i uken:
    - Omtrent hver dag:
101. Bruker du ofte ett eller flere av følgende medikamenter?
- Atbyl, Albyl-E, Alka-Seltzer, Antineuralgica, Diprin, Globentyl, Globoid, Paraflex eller Paraflex comp.: ........................................ (Sett kryss i den ruten som passer)

102. Bruker du ofte ett eller flere av følgende medikamenter?
- Brufen, Clinoril, Confortid, Donobid, Felden, Indocid, Napren, Napren-E eller Naprosyn: ........................................ (Sett kryss i den ruten som passer)

103. Bruker du ofte sovedisiner? ........................................ (Sett kryss i den ruten som passer)

104. Bruker du ofte nornedisiner? ........................................ (Sett kryss i den ruten som passer)

105. Nåværende hovedyta:

- Hjemmeværende husmor: ........................................ 105.1
- Skoleelever/student: ........................................ 105.2
- Industriverksted/anleggs/bygnings/sprengnings/gruearbeide: ........................................ 105.3
- Jordbruk/skogbruksarbeide: ........................................ 105.4
- Fisker/sjømann: ........................................ 105.5
- Kontor/handels/hotell/servicearbeide: ........................................ 105.6
- Helse/tører/annet undervisningsarbeide: ........................................ 105.7
- Landtransport (sjåfor m.v.): ........................................ 105.8
- Arbeidssledig: ........................................ 105.9
- Under atferd: ........................................ 105.10
- Uferdetygd/alderstrygd/pensjonert: ........................................ 105.11
- Annet: ........................................ 105.12
- Angi evl. yrkesbetegnelse her:

106. Har du skiftarbeide? ........................................ (Sett kryss i den ruten som passer)

107. Angi antall år du har vært på din siste arbeidsplass: ........................................ 107

108. Må du i forbindelse med arbeide/skolegang overnattet utenfor hjemmet? ........................................ (Sett kryss i den ruten som passer)

109. Hvis "JA", hvordan overnatter du?

- I ordinær bopelse/pleie: ........................................ 109.1
- På hotel/pensjonert: ........................................ 109.2
- På hybel: ........................................ 109.3
- I anleggsbunkere: ........................................ 109.4
- På annen måte: ........................................ 109.5

111. Angi hvor mange års skolegang du har medregnet folkeskole og framskilt skole eller 9-års grunnskole?

112. Angi antall familiemedlemmer (deg selv medregnet) som bor i din husstand:

113. Er noen i din husstand 10 år eller yngre? ........................................ (Sett kryss i den ruten som passer)

114. Trenger noen i din husstand utenom barna spesielt tilsyn eller pleie? ........................................ (Sett kryss i den ruten som passer)

115. Hvordan var de økonomiske forhold i familien under oppveksten din?

- Meget gode: ........................................
- Gode: ........................................
- Vanskelige: ........................................
- Meget vanskelige: ........................................

116. Hvordan vil du beskrive din økonomiske situasjon nå?

- Meget god: ........................................
- Gode: ........................................
- Vanskelig: ........................................
- Meget vanskelig: ........................................

117. Har du de siste to månedene falt deg ute av stand til å måle dine vanskeligheter?

- Aldri eller sjelden: ........................................
- Av og til: ........................................
- Ofte: ........................................
- Nesten hele tiden: ........................................

118. Har du de siste to månedene falt deg «nedfor»?

- Aldri eller sjelden: ........................................
- Av og til: ........................................
- Ofte: ........................................
- Nesten hele tiden: ........................................

119. Føler du at du har dårlig tid, også når det gjelder daglige gjennomlag?

- Aldri eller sjelden: ........................................
- Av og til: ........................................
- Ofte: ........................................
- Nesten hele tiden: ........................................