## **CONTENTS**

	raye
Abstract	V
Acknowledgements	viii
Contents	x
List of Abbreviations	xix
List of Tables	xxii
List of Figures	xxiv
CHAPTER 01. INTRODUCTION	1 – 30
1.1 Anatomy and Physiology of the Upper Gastrointestinal Tract	2 – 11
1.1.1 Oesophagus	2
1.1.1.1 Gross anatomy of the oesophagus	2
1.1.1.2 Microstructure of the oesophagus	3
1.1.1.3 Lower oesophageal sphincter	4
1.1.2 Stomach	4
1.1.2.1 Gross anatomy of the stomach	4
1.1.2.2 The sphincters of the stomach	5
1.1.2.3 Gastro-oesophageal junction	6
1.1.2.4 Microstructure of the stomach	6
1.1.3 Duodenum	9
1.1.3.1 Gross anatomy of the duodenum	9
1.1.3.2 Microstructure of the duodenum	9
1.2 Abnormalities of the Upper Gastrointestinal Tract	11 - 23
1.2.1 Abnormalities of the oesophagus	11
1.2.1.1 Gastro-oesophageal reflux disease	11
1.2.1.2 Oesophageal motor disorders	12
1.2.1.3 Abnormalities of oesophageal anatomy	13
1.2.1.4 Extrinsic oesophageal compression	14
1.2.1.5 Trauma to the oesophagus	15

	1.2.1.6 Oesophageal neoplasms	16
	1.2.1.7 Esophageal mucosal diseases	17
1.	2.2 Abnormalities of the stomach	18
	1.2.2.1Gastritis	18
	1.2.2.2 Peptic ulcer disease	19
	1.2.2.3 Gastric polyps	20
	1.2.2.4 Gastric carcinoma	21
	1.2.2.5 Gastric MALT lymphoma	22
1.	2.3 Abnormalities of the duodenum	22
	2.3.1.1 Duodenitis and Duodenal ulcers	22
1	.2.4 Non-ulcer dyspepsia	23
1.3 U	pper Gastrointestinal Abnormalities in a Referred Population	23 – 28
CHAPTER 02	2. LITRETURE REVIEW	31 - 74
2.1 <i>H</i>	elicobacter pylori and Upper Gastrointestinal Disease	32 - 51
2.	1.1 Role of <i>H.pylori</i> in human disease - historical evidence	32
2.	1.2 Microbiological characteristics	34
	2.1.2.1 Classification	34
	2.1.2.2 Biochemical properties and growth characteristics	35
	2.1.2.3 Outer membrane proteins (OMPs)	36
2.	1.3 Pathogenesis	38
	2.1.3.1 Virulence factors	39
j	2.1.3.2 Mechanism of tissue damage	42
	2.1.3.3 Histopathological features	43
	2.1.3.4 Carcinogenesis	46
2.	1.4 Immune response of the host	47
2.1.5 Co-relation of <i>H.pylori</i> with gastro-duodenal disease.	48	
	2.1.5.1 Peptic ulceration and chronic gastritis	48
•	2.1.5.2 Adenocarcinoma of the stomach	50
	2.1.5.3 Gastro-esophageal reflux disease	50

2.2 Transmission of <i>Helicobacter pylori</i> Infection	52 – 54
2.3 Diagnosis of Helicobacter pylori Infection	54 - 65
2.3.1 Endoscopic dependent tests	55
2.3.1.1 Histology	55
2.3.1.2 Culture	56
2.3.1.3 Rapid urease test	58
2.3.1.4 Polymerase Chain Reaction (PCR)	59
2.3.2 Non endoscopic dependent tests	60
2.3.2.1 Urea breath test	60
2.3.2.2 Serology	61
2.3.3 Other tests	64
2.3.3.1 Stool antigen test	64
2.3.3.2 String test	65
2.4 Epidemiology and Risk Factors of H. pylori Infection	
and Its Regional Variation	65 – 70
2.5 Helicobacter pylori Infection in Sri Lanka	70 – 72
OBJECTIVES	73 - 74
CHAPTER 03. MATERIALS AND METHODS	75 – 115
3.1 Upper Gastrointestinal Endoscopy	76 – 83
3.1.1 Selection of the patients for study sample	76
3.1.2 Interviewing and examination of the patients	76
3.1.2.1 Reassurance of the patients and informed consen	t 76
3.1.2.2 Risk factor assessment	77
3.1.2.2 WHO Quality of Life assessment	78
3.1.3 Preparation of the instrument	78
3.1.4 Preparation of patients and procedure	78
3.1.5 Obtaining biopsy specimens	80
3.1.6 Disinfection of upper GI endoscope	82

3.2	2 Histology	83 – 91
	3.2.1 Preparation of biopsy specimens for processing.	83
	3.2.2 Tissue processing.	84
	3.2.3 Embedding	85
	3.2.4 Section cutting	86
	3.2.5 Haematoxyline & Eosin (H & E) staining	86
	3.2.6 Modified Giemsa staining	87
	3.2.6.1 Preparation of Giemsa stain	88
	3.2.6.2 Modified Giemsa staining technique	88
	3.2.7 Examination of slides and reporting	89
	3.2.7.1 Updated Sydney Classification -morphological limb	90
3.3	Culture	91 – 96
	3.3.1 Preparation of culture medium	92
	3.3.2 Inoculation of biopsy specimens	93
	3.3.3 Examination of cultures	93
	3.3.3.1 Colony morphology	94
	3.3.3.2 Biochemical testing	94
	3.3.3.3 Modified Gram stain for identification of colonies	95
3.4	Rapid urease test (CLO test)	96 – 98
	4.3.1 Preparation of urea solution	96
	4.3.2 Method of examination and interpretation of results	98
3.5	Serology	98 – 105
	3.5.1 Collection of blood samples	98
	3.5.2 Plasma separation	98
	3.5.3 Detection of <i>H.pylori</i> IgG in human plasma	99
	3.5.3.1 Contents of the test kit	99
	3.5.3.2 Dilution of plasma samples	100
	3.5.3.3 Preparation of working wash solution	100
	3.5.3.4 Procedure	101

3.5.3.5 Measurement of absorbance using the	
ELISA microplate reader	103
3.5.4. Detection of <i>H.pylori</i> IgA in human plasma	104
3.5.4.1 Contents of the test kit	104
3.5.4.2 Procedure	104
3.6 Selection of cases and controls for three case-control studies	105 - 106
3.7 Selection of cases and controls for assessment	
of Quality of Life	106
3.8 Statistical Analysis	106 – 108
3.6.1 Calculation of the sample size	107
3.6.1.1 Calculation of the sample size to study	
the <i>H.pylori</i> prevalence	107
3.6.1.2 Calculation of the sample size for the	
case control study	107
CHAPTER 04. RESULTS	116 – 155
4.1 The pattern of endoscopically detected abnormalities among	
patients in the study sample	117 – 121
4.1.1 Oesophageal abnormalities	117
4.1.2 Gastric abnormalities	119
4.1.3 Duodenal abnormalities	121
4.2 Histological abnormalities among subjects in the	
study sample and the correlation between endoscopic	
and histological abnormalities	121 – 125
4.2.1 Histological abnormalities	121
4.2.1.1 Histological abnormalities of the oesophagus	121
4.2.1.2 Histological abnormalities of the stomach	122
4.2.1.3 Histological abnormalities of the duodenum	123

4.2.2 Correlation between histological abnormalities	
and endoscopically detected abnormalities	123
4.2.2.1 Correlation between histological gastritis	
and endoscopically detected gatritis	123
4.2.2.2 Correlation between histology and endoscopy	
in detecting chronic gastric ulcers	125
4.3 Description of the histological changes of	
gastric mucosa and H.pylori status according	
to Sydney Classification	125 - 126
4.3.1 Classification of the antral histological	
findings and <i>H.pylori</i> status	126
4.3.2 Classification of the corporal histological	
findings and <i>H.pylori</i> status	126
4.4 The prevalence of <i>H. pylori</i> infection	127 – 132
4.4.1 Prevalence of <i>H.pylori</i> among different	
disease categories determined by endoscopy	128
4.4.1.1 Oesophagus	128
4.4.1.2 Stomach	129
4.4.1.3 Duodenum	130
4.4.2 Prevalence of <i>H.pylori</i> among different	
disease categories determined by histology	131
4.4.2.1 Oesophagus	131
4.4.2.2 Stomach	131
4.2.2.3 Duodenum	132
4.5 Determination of the best biopsy site to interpret the	
histological abnormalities in the gastric mucosa and	
to detect the presence of <i>H.pylori</i> infection	133 – 135

for H.pylori	135 – 136
4.7 Socio-economic status, social habits, eating pattern, drug usa	age,
living conditions in patients with peptic ulcer disease,	
gastritis, or gastro-esophageal reflux disease: analysis	
of three case-control studies	136 – 152
4.7.1 Peptic ulcer disease	136
4.7.2 Gastro-esophageal reflux disease	142
4.7.3 Gastritis	146
4.8 Comparison of the Quality of Life of patients with	
upper gastrointestinal symptoms with a Control group	152 – 156
4.8.1 Comparison of quality of life (QOL) between	
patients and controls	152
4.8.2 The effect of alcohol consumption on quality	
of life within the patient group	153
4.8.3 The effect of density of <i>H.pylori</i> colonization	
on quality of life	154
CHAPTER 05. DISCUSSION	157 – 195
5.1 The pattern of endoscopic abnormalities in patients	
referred for gastroscopy	158 – 162
5.1.1 Oesophageal abnormalities	159
5.1.2 Gastric abnormalities	160
5.1.3 Duodenal abnormalities	161
5. 2 The pattern of histological abnormalities among patients	
in the study sample and the correlation between	
endoscopic and histological abnormalities	162 – 165

4.6 Sensitivity and specificity of diagnostic tests

5.3	B Prevalence of <i>H.pylori</i> among different disease categories	166 – 175
	5.3.1 Prevalence of <i>H.pylori</i> in oesophageal abnormalities	168
	5.3.2 Prevalence of <i>H.pylori</i> in gastric abnormalities	171
	5.3.3 Prevalence of <i>H.pylori</i> in duodenal abnormalities	174
5.4	Description of the histological changes of gastric mucosa	
	and H.pylori status according to Sydney Classification	175 – 177
5. 5	5 Determination of the best biopsy site to interpret the	
	histological abnormalities in the gastric mucosa and to	
	detect the presence of <i>H.pylori</i> infection	177 – 178
5.6	Sensitivity and specificity of commonly used diagnostic	
	tests in detecting H.pylori infection	179 – 184
	5.6.1 Gold standard in the diagnosis of <i>H.pylori</i>	179
	5.6.2 Sensitivity and specificity of H & E and Modified Giemsa	179
	5.6.3 Sensitivity and specificity of rapid urease test	180
	5.6.4 Sensitivity and specificity of serology	181
	5.6.5 Sensitivity and specificity of culture	183
5.7	Comparing the cost of different diagnostic techniques	185 – 187
5.8	Comparison of socioeconomic status, habits, food practices,	
	drug usage, living conditions and personal hygiene in	
	patients with peptic ulcer disease, gastro-oesophageal reflux	
	disease and gastrits: Three case control studies.	187 – 194
	5.8.1 Risk and protective factors of peptic ulcer disease	188
	5.8.2 Risk and protective factors of gastro-oesophageal	
	reflux disease	189
	5.8.3 Risk and protective factors of gastritis	191
5.9	Assessment of the Quality of life of the patients	
	presented with upper gastrointestinal symptoms and	
	comparison with an ago and say matched control group	104 _ 106

CONCLUSIONS AND RECOMMENDATIONS	197
LIMITATIONS	201
REFERENCES	203
ANNEXURES	246

## LIST OF ABBREVIATIONS

cm centimetre

mm millimetre

in inch

ml millilitre

L litre

kg kilogram

g gram

mg milligram

WHO QOL BREF Word Health Organization Quality of Life -

abbreviated version

H&E Haematoxyline and Eosin

H<sub>2</sub>O<sub>2</sub> Hydrogen peroxide

RAC Regular Arrangement of Collecting venule

US United States

UK United Kingdom

GSRS Gastrointestinal Symptom Rating Scale

QOLRAD Quality of Life in Reflux and Dyspepsia

HRQOL Health related Quality of Life

NSAIDs Non Steroidal Anti-Inflammatory Drugs

CLO Campylobacter Like Organism test

GORD Gastro-oesophageal reflux disease

GI Gastrointestinal

UGIE Upper Gastro Inestinal Endoscopy

Fig Figure

BHT Bead Head Ticket

EDTA Ethylene Diamine Tetra Acetic acid

ELISA Enzyme Linked Immunosorbent Assay

IgA Immunoglobulin A

IgG Immunoglobulin G

TMB tetramethylbenzidin

OGD Oesophago Gastro Duodenoscopy

H.pylori Helicobacobacter pylori

ASGE American Society of Gastroentrology

OPD Out Patients Department

Cag A Cytotoxin associated gene product A

Vac A Vacuolating cytotoxin

HpSS *H.pylori* Silver Stain

PCR Polymerase Chain Reaction

SBA Sheep Blood Agar

SM Skirrow medium

HpCA H.pylori Circulating Antigen

NAP Neutrophil Activating Protein

NF-Kb Nuclear Factor Kb

Pal Pathogenicity Island

IL-8 Interleukin 8

Oip A Outer Inflammatory protein A

Hsp 60 Heat shock protein 60

MALT Mucosa Associated Lymphoid tissue

IFN Interferon

TGF Transforming Growth Factor

T4 SS Type IV Secretory System

Th1 response T1 helper cell response

DNA Deoxyribonucleic acid

OMP Outer membrane protien

MHC Major Histocompatibility Complex

HCO<sub>3</sub> Bicarbonate ion

G gauge

SD standerd deviation

LPS Lipopopolysaccharide

H<sub>2</sub>O Water

CO<sub>2</sub> Carbon dioxide

N<sub>2</sub> Nitrogen

(NH<sub>2</sub>)<sub>2</sub>CO Urea

NH<sub>3</sub> Ammonia

NH<sub>4</sub><sup>+</sup> Ammonium ions

## LIST OF TABLES

- Table 4.1: The number (%) of oesophageal abnormalities detected in 251 patients who underwent endoscopy
- Table 4.2: The frequency distribution of severity in 45 patients detected to have erosive oesophagitis
- Table 4.3: The frequency distribution of the severity in 19 patients detected to have varices
- Table 4.4: The number (%) of gastric abnormalities detected in 251 patients who underwent endoscopy
- Table 4.5: The frequency distribution of topography of gastritis in 73 patients detected to have gastritis endoscopically
- Table 4.6: The number (%) of duodenal abnormalities detected in 251 patients who underwent endoscopy
- Table 4.7: The number (%) of histological abnormalities detected in the esophagus
- Table 4.8: The frequency distribution of topography of histological gastritis
- Table 4.9: Association between histological chronic gastritis and endoscopic chronic gastritis
- Table 4.10: Agreement between topography of histological gastritis and topography of endoscopic gastritis
- Table 4.11: The frequency distribution of histology of chronic gastric ulcers
- Table 4.12: Endoscopic abnormalities of the oesophagus and the prevalence of H.pylori
- Table 4.13: Endoscopic abnormalities of the stomach and the prevalence of *H.pylori*
- Table 4.14: Prevalence of *H.pylori* according to the distribution of gastritis endoscopically
- Table 4.15: Endoscopic abnormalities of the duodenum and the prevalence of *H.pylori*
- Table 4.16: Histological abnormalities of the oesophagus and the prevalence of *H.pylori*
- Table 4.17: Histological abnormalities of the stomach and the prevalence of *H.pylori*
- Table 4.18: Prevalence of *H.pylori* according to the distribution of gastritis histologically
- Table 4.19: Histological abnormalities of the duodenum and the prevalence of *H.pylori*

- Table 4.20: The sensitivity and positivity of different indices in detecting *H.pylori* infection
- Table 4.21: Sensitivity and specificity of main histological abnormalities in antrum and corpus
- Table 4.22: Sensitivity and specificity of different tests in detecting *H.pylori* infection
- Table 4.23: Socio economic status, physical activities and personal hygienic among patients with peptic ulcer disease and controls
- Table 4.24: Social habits among patients with peptic ulcer disease and controls
- Table 4.25: Drug usage among patients with peptic ulcer disease and controls
- Table 4.26: food habits among patients with peptic ulcer disease and controls
- Table 4.27: Height, weight and cardiovascular measurements among cases and controls\*
- Table 4.28: Socio economic status, physical activities and personal hygienic among patients with GORD and controls
- Table 4.29: Social habits among patients with GORD and controls
- Table 4.30: Drug usage among patients with GORD and controls
- Table 4.31: Food habits among patients with GORD and controls
- Table 4.32: Height, weight and cardiovascular measurements among cases and controls
- Table 4.33: Socio economic status, physical activities and personal hygienic among patients with gastritis and controls
- Table 4.34: Social habits among patients with gastritis and controls
- Table 4.35: Drug usage among patients with gastritis and controls
- Table 4.36: Food habits among patients with gastritis and controls
- Table 4.37: Weight, height and cardiovascular measurements among cases and controls\*
- Table 4.38: Comparison of the quality of life of patients with upper gastrointestinal symptoms and the control group on the dimensions of the WHOQOL-BREF
- Table 4.39: Effect of alcohol consumption on the quality of life among the symptomatic patients as assessed by the WHOQOL-BREF
- Table 4.40: Effect of the *H.pylori* density on the quality of life among the symptomatic patients

## LIST OF FIGURES

- Figure 2.1 a: Anatomy of the Stomach. b: Gastro-oesophageal junction
- Figure 2.2 Normal gastric mucosa a. cardiac region b. fundus / body c. antrum
- Figure 3.1 Light microscopic appearance of normal gastric antrum (H& E 10X10)
- Figure 3.2 Light microscopic appearance of normal gastric corpus (H& E 10X10)
- Figure 3.3 Light microscopic appearance of gastric antrum with mild chronic inflammation (H&E 10X10)
- Figure 3.4 Light microscopic appearance of gastric corpus with mild chronic inflammation (H&E 10x10)
- Figure 3.5 Light microscopic appearance of gastric antrum with severe chronic inflammation (H&E 10x10)
- Figure 3.6 Light microscopic appearance of gastric antrum with gastric atrophy (H&E10x10)
- Figure 3.7a Light microscopic appearance antral gland with *H.pylori* (H&E10X40)
- Figure 3.7b Light microscopic appearance antral gland with *H.pylori* (H&E 10X 40)
- Figure 3.8a Light microscopic appearance antral gland with *H.pylori*(Modified Giemsa 10X 40)
- Figure 3.8b Light microscopic appearance antral gland with *H.pylori*(Modified Giemsa 10X40)
- Figure 3.9 *H.pylori* in a smear obtained from culture (Modified Gram Stain 10X100)
- Figure 3.10 Positive rapid urease reaction