HELICOBACTER PYLORI:
ITS ROLE IN THE AETIOLOGY OF NON-ULCER
DYSPEPSIA IN NORTHERN NIGERIA

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Thesis for the Degree of MD

London University
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ABSTRACT

In a pilot study dyspepsia was found to account for 20/1,000 admissions at the University of Maiduguri Teaching Hospital, in Northern Nigeria, the majority of these patients had non-ulcer dyspepsia. In a prospective study of patients presenting with carefully defined non-ulcer dyspepsia 53 of 57 patients had gastritis and of these 46/53 (87%) were infected by the bacteria Helicobacter pylori (H.pylori).

As a result of this pilot study and a subsequent review of the literature it was hypothesised that H.pylori is the cause of non-ulcer dyspepsia in northern Nigeria.

The strong association of H.pylori with non-ulcer dyspepsia was confirmed in a prospective study of 138 patients, 126 (91%) of whom had gastritis and of these 120 (95%) were infected by H.pylori.

However this high prevalence of H.pylori infection must be judged against the prevalence of infection in the general population. In a random serological survey 228/268 (85%) subjects over 5 years had IgG antibodies to H.pylori. This is not significantly different from that found in patients with non-ulcer dyspepsia (87%). H.pylori infection was also present in 80% of 40 asymptomatic volunteers.

H.pylori acting alone does not cause non-ulcer dyspepsia, but may play a role in combination with other factors. If this is the case, clearance of the organism should lead to improvement or resolution of symptoms.

Therefore 130 patients were entered into a therapeutic trial of a combination antacid (Gelusil) one tablet four times a day versus an anti-H.pylori regime (DeNol 240 mg four times a day and amoxycillin, 500mg four times a day.
day for the first 14 days). One hundred and nine patients were reassessed at the end of treatment. Symptoms completely resolved in 1 of 23 patients (4.4%) who had taken Gelusil and 28 of 86 (32%) of patients who had taken bismuth & amoxycillin, a statistically significant difference (p<0.01). However, resolution of symptoms was not related to \textit{H.pylori} clearance.

These studies do not provide any evidence to support a role for \textit{H.pylori} in the cause of non-ulcer dyspepsia in northern Nigeria, thus disproving the hypothesis.
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Principle criterion of response: symptom resolution according to \textit{H.pylori} status.
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37 Symptom score according to *H. pylori* status after treatment with bismuth & amoxycillin.
Northern Nigeria is a distinct geographical area, characterised by high temperatures and low rainfall, and a predominantly Muslim population. There is very little literature available on dyspepsia in this area, but what there is (Tovey & Tunstall, 1974) suggests that dyspepsia and peptic ulceration is uncommon.

Contrary to this impression large numbers of patients attend the outpatient department at the University of Maiduguri Teaching Hospital with dyspepsia. Most of these patients are given a clinical diagnosis of peptic ulcer, but this is often not confirmed (see part 2 of pilot study, page 16) and a large proportion of these patients have non-ulcer dyspepsia (see part 5 of pilot study, page 30).

Helicobacter pylori, discovered by Warren and Marshall in 1983, causes type B antral gastritis (Warren & Marshall, 1983) and it has been suggested that it plays a role in the aetiology of non-ulcer dyspepsia (see literature review, page 78). However this work has been done largely in the 'West' (see footnote), where the population structure, social and living conditions, disease patterns and H. pylori infection profile differ markedly from the 'Developing World' (see footnote), so that research findings from the 'West' cannot be automatically applied to the 'Developing World'.

This thesis addresses the question of the role of H. pylori in the aetiology of non-ulcer dyspepsia in the 'Developing World' and specifically in NE Nigeria.

Footnote: Definitions

Developing World: Countries with a relatively low per capita income, high population growth and poor health care. Most countries in Africa, South America and Asia.

The West: Industrialised countries, with a relatively high per capita income, low population growth and good health care; Western Europe, North America, Australasia and Japan.
Fig. 1. Map of Africa
CHAPTER ONE

PILOT STUDY
OUTLINE OF PILOT STUDY

1) Introduction.

2) Incidence and Cause of Dyspepsia amongst Hospital Inpatients.

3) Incidence of Dyspepsia presenting to Rural Health Centres in North East Nigeria.

4) Prevalence of Dyspepsia in the Rural Community: A Random Survey.

5) Prospective Study of Patients presenting with Dyspepsia: Initial Findings.

6) Conclusion.
INTRODUCTION

The University of Maiduguri Teaching Hospital is a, recently built, 500 bed teaching hospital in the northern savannah of Nigeria. This is a distinct geographical area characterised by high temperatures, low rainfall and low humidity (see figures 2 & 3). The land is mainly poor quality scrub lying just south of the true desert, with a predominantly Muslim population. The founding of a university teaching hospital provides the opportunity for research in an area in which very little has previously been done.

Fig.2. Nigeria: mean annual rainfall
Fig. 3. West Africa: seasonal temperatures and air currents.

TEMPERATURE

JANUARY

SURFACE TEMPERATURE

JULY

WINDS

NOV-MARCH

HARMATTAN

APRIL-OCTOBER

SOUTH-WEST MONSOON
Patients commonly present to the University of Maiduguri Teaching Hospital with dyspepsia, yet the cause of this and the most appropriate treatment are unknown. Most patients have a history of several years. Many have been admitted to hospital and have spent considerable sums of money on medication, often in excess of N1,000 which is the equivalent of five months wages for a labourer. Patients were generally given a clinical diagnosis of peptic ulcer, but in most this was not proven by investigation.

These patients are all the more striking as the published literature suggests that peptic ulcer is rare in the dry northern savannah (Konstam, 1954, Tovey and Tunstall, 1975).

Further to these initial observations a four part pilot study was carried out:

1) A Retrospective review of all patients admitted with dyspepsia during 4 years, 1984-1987, in order to establish the incidence of admission for dyspepsia and the definitive diagnosis in these patients.

2) A review was made of the clinical diagnoses of patients presenting to 6 rural health centres in Borno State during 1987. This was necessary in order to ascertain that dyspepsia was common in a more representative sample of the population than that provided by the teaching hospital.

3) A random population survey was carried out in five villages close to Maiduguri, to determine the true prevalence of dyspepsia. A random survey is essential as many people with dyspepsia do not present for formal medical care (Jones & Lydeard, 1989).

4) Finally a prospective study using a questionnaire, gastroscopy and biopsy, was conducted on patients presenting to the teaching hospital with chronic dyspepsia, in order to gather data on the possible causes of dyspepsia in this environment.
INTRODUCTION

Konstam in 1954 was the first to suggest that peptic ulcer was rare in the dry, northern savannah of Nigeria, a finding confirmed by Tovey and Tunstall in 1975. Nevertheless large numbers of patients present to the teaching hospital with dyspepsia, in apparent contradiction of the published data.

The widely quoted paper of Tovey and Tunstall (1975) on duodenal ulcer in black populations south of the Sahara was based on hospital inpatient data. However, many hospitals at this time, did not have facilities for barium meal examination; the diagnosis was often dependent on surgery in those with complications of their peptic ulcer, thus excluding those with uncomplicated ulcer and non-ulcer dyspepsia.

The opening of the teaching hospital in Maiduguri in 1982, with its well equipped X-ray department, allowed the definitive diagnosis of ulcer and non-ulcer dyspepsia in those without complications. This study was carried out to assess the incidence of admission for dyspepsia at the teaching hospital and to discover the diagnoses in these patients.

METHODS

The case notes were reviewed of all patients admitted as inpatients to the teaching hospital with dyspepsia over a four year period. In practice this consisted of all patients with a clinical diagnosis of peptic ulcer, duodenal ulcer or gastric ulcer.
The hospital has a good medical records department with well-trained staff and it was possible to retrieve 90% of the case notes. The hospital was planned as a tertiary referral centre for north east Nigeria, but medical facilities are limited in the rest of the region, so a large proportion of patients are seen without prior referral. The patient population is, however, biased towards the local urban population.

RESULTS

The diagnosis of peptic ulcer was made mainly on the basis of barium meal findings, performed by, and reported on, by trained radiologists. During the four year period 200 patients were admitted with dyspepsia: 60 had a duodenal ulcer confirmed by barium meal or at operation, 39 had a normal barium meal and in 101 no definite diagnosis was made; (these were usually patients who were asked to attend for outpatient barium meal, but did not return for the X-ray or further follow up).

There were a total of 9,883 adult admissions (excluding obstetrics) during the period of the study, giving an admission rate for dyspepsia of 20/1,000, and for duodenal ulcer of 6/1,000.

Those with a final diagnosis of non-ulcer dyspepsia make up 20% of the total and presumably a proportion of the patients in whom no definitive diagnosis was made, also had non-ulcer dyspepsia. The patients with non-ulcer dyspepsia had a mean age of 39, a mean length of history of 25 months and a male to female ratio of 1 to 1.3. The commonest presenting complaint was epigastric pain and the commonest sign epigastric tenderness. No particular occupation predominated, and the commonest exacerbating factors were pepper and hunger.

Of the 60 patients with duodenal ulcer (see table 1), 16 (27%) presented with complications, 10 with gastric outlet obstruction (17%), 5 with
perforation (8%) and 1 with haematemesis, a further 11 (18%) were operated on for failure of medical management. Of the remainder (33), 29 were treated with H2 blockers and 4 with antacids. The male to female ratio was 2.8 to 1 and the mean age 34 years. Most patients (77%) were from northern tribes. The mean length of history was 44 months, ranging from those who had been asymptomatic before a sudden perforation, to those with a history of over 20 years.

**Table 1:** Presenting complaint and treatment in 60 patients with duodenal ulcer

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>H2 Block</td>
</tr>
<tr>
<td>Simple ulcer</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Perforation</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Haematemesis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>60</td>
<td>30</td>
</tr>
</tbody>
</table>

Abbreviations: HSV: Highly selective vagotomy

**CONCLUSION**

This retrospective study of inpatient admissions demonstrates that dyspepsia is a common cause of hospital admission with an incidence of 20/1,000 adult admissions. This compares with Addis Ababa, in Ethiopia where the admission rate for dyspepsia was 72/1,000 (Mengesha, 1983).

Twenty percent of those admitted had a confirmed diagnosis of non-ulcer dyspepsia, an incidence of 2/1000 admissions. This compares with 65% in an endoscopy series of 1,735 patients in Ethiopia (Abebe, 1983) and a mean of 46% in 14 series reviewed by Thompson (1984). However, the patients reviewed in this series are a selected group, a large proportion of whom...
were being admitted because of failure of medical management or complications of a confirmed peptic ulcer. It is likely, therefore, that in an outpatient population the percentage with non-ulcer, rather than ulcer, dyspepsia would be higher.
INCIDENCE OF DYSPEPSIA IN PATIENTS PRESENTING TO RURAL HEALTH CENTRES IN NORTH EAST NIGERIA

INTRODUCTION

The University of Maiduguri Teaching Hospital sees a largely urban group of patients. In order to assess the incidence of dyspepsia in patients presenting for medical care in the wider rural community, the outpatient statistics from six rural health centres were analysed.

METHODS

The Church of Christ in Nigeria Rural Health Programme runs six health centres in north eastern Nigeria (see figure 4). The dispensaries are in rural areas, staffed by trained Nigerian dispensers and overseen by Dr A. Mc Neil, who supplied the data. Accurate records are kept of age, sex, presenting complaint and treatment for each patient who attends. A diagnosis of dyspepsia is made in patients presenting with epigastric pain related to meals.

RESULTS

For the year 1987 a total of 37,812 patients attended the health centres. Of these 1,537 presented with dyspepsia, giving an incidence of 4.1%. In the same year 1,342 (3.5%) patients were seen with intestinal parasites, 2,397 (6.3%) patients with dysentry and 7,071 (18.7%) with diarrhoea.
Fig. 4. Church of Christ in Nigeria rural health centres in Borno State.
Table 2: Number of patients presenting with dyspepsia, parasites, dysentry, and diarhoea in 1987.

<table>
<thead>
<tr>
<th></th>
<th>Jan</th>
<th>Feb</th>
<th>Mar</th>
<th>Apr</th>
<th>May</th>
<th>Jun</th>
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<th>Sep</th>
<th>Oct</th>
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<tr>
<td>Dyspepsia</td>
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<td>124</td>
<td>116</td>
<td>127</td>
<td>116</td>
<td>144</td>
<td>157</td>
<td>241</td>
<td>179</td>
<td>102</td>
<td>74</td>
<td>38</td>
</tr>
<tr>
<td>Incidence %</td>
<td>5.0%</td>
<td>4.0%</td>
<td>3.2%</td>
<td>3.8%</td>
<td>4.5%</td>
<td>3.7%</td>
<td>3.9%</td>
<td>7.3%</td>
<td>4.6%</td>
<td>3.4%</td>
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<td>1.5%</td>
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<tr>
<td>Parasites</td>
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<td>88</td>
<td>91</td>
<td>122</td>
<td>158</td>
<td>136</td>
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<td>Incidence %</td>
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<td>Dysentry</td>
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<td>171</td>
<td>180</td>
<td>213</td>
<td>345</td>
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<td>Incidence %</td>
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<td>8.3%</td>
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<td>Diarhoea</td>
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<td>507</td>
<td>647</td>
<td>523</td>
<td>586</td>
<td>780</td>
<td>810</td>
<td>715</td>
<td>341</td>
<td>590</td>
<td>511</td>
<td>569</td>
</tr>
<tr>
<td>Incidence %</td>
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<td>16%</td>
<td>18%</td>
<td>16%</td>
<td>23%</td>
<td>20%</td>
<td>20%</td>
<td>22%</td>
<td>9%</td>
<td>20%</td>
<td>23%</td>
<td>23%</td>
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<tr>
<td>Total No. Consultations</td>
<td>2373</td>
<td>3119</td>
<td>3637</td>
<td>3344</td>
<td>2565</td>
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<td>3316</td>
<td>3859</td>
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<td>2218</td>
<td>2493</td>
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</table>

Fig.5. Monthly incidence of dyspepsia & parasites.

MONTHLY INCIDENCE OF DYSPEPSIA AND PARASITES
DISCUSSION

Dyspepsia accounts for 4.1% of consultations to rural health centres in north east Nigeria. This compares with 3.5% in Ethiopia (Mengeshe, 1983) and is remarkably similar to the United Kingdom where dyspepsia accounts for 3-4% of general practitioner consultations (Jones and Lydeard, 1989).

Interestingly, there is a marked difference in the number of patients presenting with dyspepsia from month to month (see table 2), varying from 38 in December (1.5% of all consultations) to 241 in August (7.3% of all consultations). This variation parallels that seen in the number of patients presenting with intestinal parasites (see figure 5). The reason for this is unknown. It could be that the intestinal parasites are the cause of the dyspepsia (see literature review, page 88) or another seasonal, independent variable that also changes in the same way may be responsible. Conceivably there may be a seasonal variation in infection by *H. pylori*, although this is pure speculation. However it is clear from this small study that before labelling a patient with a diagnosis of non-ulcer dyspepsia, in this environment it is important to consider intestinal parasites as a possible cause for the pain.
PREVALENCE OF DYSPEPSIA IN THE RURAL COMMUNITY

INTRODUCTION

Dyspepsia is a common symptom worldwide accounting for enormous morbidity and cost to the health care system (see literature review, pg.39). The prevalence of dyspepsia in the 'Developing World' is poorly documented and there have been very few population based, random studies to assess its true prevalence. Mengesha (1983) from Addis Ababa, in Ethiopia records an incidence of 3.5% in patients presenting to health centres, increasing to 17.5% of patients presenting to the teaching hospital outpatient department. However not all patients with dyspepsia present for medical care (Jones and Lydeard, 1989) and these hospital based figures are likely to underestimate the true prevalence. This study was carried out to ascertain the true prevalence of dyspepsia in a randomly chosen rural population.

METHODS

Five villages close to the state capital Maiduguri were surveyed. Houses in these villages had been previously numbered in preparation for the government’s primary health care scheme making random selection of households to be interviewed relatively easy. Occupants over five years of age were interviewed by medical students, with the help of village health workers as interpreters, using a questionnaire documenting basic demography, dyspeptic symptoms, length of history and possible aetiological factors (see Appendix 4 pg 155). The questionnaire was first tested on a group of subjects in Maiduguri. Dyspepsia was defined as epigastric pain related to meals (see definition pg 97).
RESULTS

620 subjects were interviewed, 345 males and 275 females, aged 5-80 with a mean age of 27 years. The age distribution of the sample is shown in figure 6. This is typical for the 'Developing World', with three quarters of the sample aged less than 30. 59% of the sample were either farmers or housewives. The staple food was millet, which was eaten by 86%, small amounts of guinea corn and rice were also eaten. All the subjects were from northern Nigeria, mostly from the Kanuri ethnic group (81%).

Fig.6. Age distribution of sample population.

DYSPEPSIA

Twenty six percent (80) of adult subjects (over 20 years of age) had experienced dyspepsia in the preceding six months, a further 2% (13) in the more distant past (see figure 7). Six percent (11) of teenagers and 2% (2) of children aged 5-10 years had also had dyspepsia. There were 56 males and 37 females in this group. The length of history varied from one month to over ten years with a mean of almost four years (46 months) (see figure 8). The age specific rate of dyspepsia increased with age, although the numbers at the upper end of the age range were small (see figure 9).
Fig. 7. Adult prevalence of dyspepsia.

Fig. 8. Length of history of subjects with dyspepsia.

Fig. 9. Age specific rate of dyspepsia.
Of the 93 subjects who had dyspepsia, in 52 (55%) it was severe enough for them to have sought medical advice, this was usually from traditional healers (35 subjects), who most often prescribed potash which generally gave the patients good temporary relief from their symptoms. In 37 (49%) the symptoms were severe enough to stop the subjects' normal daily activity. The commonest exacerbating factor was hunger. The frequency of the pain varied markedly between subjects, but 87% had experienced pain at least once in the preceding four weeks with 6% experiencing pain every day.

There was no difference in the type of food eaten, or occupations of those who did, and did not have dyspepsia. Alcohol intake, Cola nut ingestion, (a locally available stimulant containing caffeine), smoking and the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) were all more common in those with dyspepsia than those without (see table 3). However, the association only reached statistical significance in the case of alcohol, (p<0.0054, odds ratio 2.50) and Cola nut ingestion (p<0.00013, odds ratio 2.85).

Table 3: The Relationship between dyspepsia and alcohol intake, smoking, non-steroidal anti-inflammatory drugs and Cola nut ingestion.

<table>
<thead>
<tr>
<th></th>
<th>No Dyspepsia</th>
<th>Dyspepsia</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>34/527 (6%)</td>
<td>14/93 (15%)</td>
<td>&lt;0.0054</td>
</tr>
<tr>
<td>Smoking</td>
<td>55/527 (10%)</td>
<td>10/93 (11%)</td>
<td>&lt;0.926(ns)</td>
</tr>
<tr>
<td>NSAID Ingestion</td>
<td>139/527 (26%)</td>
<td>27/93 (29%)</td>
<td>&lt;0.593(ns)</td>
</tr>
<tr>
<td>Cola nut Ingestion</td>
<td>322/527 (61%)</td>
<td>76/93 (82%)</td>
<td>&lt;0.00013</td>
</tr>
</tbody>
</table>

ns: not significant, NSAID: Non steroidal anti-inflammatory drug.
DISCUSSION

The most important finding was a six month prevalence of dyspepsia amongst adults in north east Nigeria of 26%. This represents a significant cause of morbidity, contrary to previous impressions (Tovey and Tunstall, 1975) and confirms that dyspepsia is common in this population.

This prevalence is remarkably similar to that found in the 'West' where prevalence rates varying from 25-38% have been reported (Jones and Lydeard, 1989, Doll et al, 1951, Weir & Backet, 1968). A prevalence of 6% was found amongst teenagers a group not normally studied, but, because of the age distribution of the population, constituting a large number of subjects.

Mengesha (1983) found an incidence of dyspepsia of 17% in over 14,000 outpatients in Addis Ababa, and 4.8% of one and a half million patients presenting to health posts scattered throughout Ethiopia. However, this survey only recorded those who had sought formal health care and is likely to be a considerable underestimation as compared with the prevalence found in a random community survey. This random study as well as others (Jones and Lydeard, 1989) have shown that many people never seek medical advice. This study also shows that many who do seek advice in this environment go to traditional healers and not to formally trained health workers.

The age specific rate of dyspepsia increased with age, reaching 100% over 60, (although the numbers over 60 are very small), (see figure 9). This is contrary to the findings of Jones and Lydeard (1989) who found that the frequency of dyspepsia decreased with age.

The traditional healers use potash to treat dyspepsia and most patients found this effective. However the disadvantage of this is that those with more serious pathology would not be referred and would as a consequence be diagnosed late. As found in other studies in Africa, (Mengesha, 1983, Wyatt
et al, 1987, Stahel et al, 1981) the subjects had suffered with dyspepsia for a long time, with a mean of almost four years in this study (see figure 8).

Alcohol and Cola nut ingestion were both significantly associated with dyspepsia (see table 3). Cola nut (Cola nitida) contains caffeine, theophylline and theobromine (Ibu, et al, 1986), it is a mildly addictive stimulant widely available locally. It is analogous to coffee which has been previously implicated in the cause of non-ulcer dyspepsia (Talley and Phillips, 1988). The alcohol that is drunk in this area is usually burukutu, fermented from sorghum and locally made gin, both of which have a high alcohol content. In this study no association has been shown between dyspepsia and smoking or non-steroidal anti-inflammatory drug ingestion.

COMMENT

Dyspepsia is a common symptom in north east Nigeria and is not confined only to the select group of patients seen at the teaching hospital. It is estimated that the population of Borno is 4.089 million, suggesting that over one million people are suffering from dyspepsia, a problem of considerable importance!
INTRODUCTION

Dyspepsia is a common cause of admission to hospital, of presentation at rural health centres and is common amongst the population at large. Most of the patients seen at the teaching hospital are given a clinical diagnosis of peptic ulceration, however this is notoriously unreliable (Anonymous editorial, 1986, Mengitsu, 1983) and only 60 of 200 inpatients given a diagnosis of peptic ulcer at the teaching hospital had this confirmed.

The following prospective study was carried out to investigate these patients in more detail and to establish a definitive diagnosis in those presenting with dyspepsia.

METHODS

57 patients presenting to the outpatient department University of Maiduguri Teaching Hospital with chronic dyspepsia (see definition pg 97) were studied. Each patient had a standard proforma completed, which gave basic demographic details and characterised the dyspepsia. Each patient underwent day case upper gastrointestinal endoscopy at which three biopsies were taken, two from the antrum and one from the body of the stomach. One biopsy from the antrum was taken for microscopy and culture, the other two biopsies were sent for histology. The specimens for histology were fixed in formalin, stained with haematoxylin and eosin and examined for the presence of Helicobacter-like organisms and gastritis (see chapter 4 for details, pg 96 ff).

Symptom Scoring

As part of this study the questionnaire (see appendix 4, pg.155) and method of symptom scoring were tested. The on study forms and questionnaires were filled in by me. An interpreter was required, and on occasions considerable persistence was required to ensure patients understood the questions and to clarify the patient's symptoms. The questionnaires were modified during the pilot study to the understanding of the patients, for example it was very difficult to make the patients understand early post prandial saitey and this question was omitted. Vague patients were given diary cards to complete.

A standard, well validated method of scoring the symptoms of non-
ulcer dyspepsia does not exist. The method of scoring outlined below arbitrarily scores the main symptoms of dyspepsia, with particular emphasis on their severity. The problems inherent in the scoring of dyspepsia were recognised and therefore the primary criterion of response was set as the complete resolution of symptoms. The symptom score was only used as a subsidiary criterion of response, although it did prove sensitive in responding to symptom improvement. Those who when questioned felt much better, had a greater improvement in symptom score than those who had improved only a little and those who felt worse whose symptom scores increased. The following symptoms and their features were used to compile a symptom score, as follows:

<table>
<thead>
<tr>
<th>SYMPTOM SCORE VALUES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of pain Mins</td>
</tr>
<tr>
<td>&lt;5</td>
</tr>
<tr>
<td>5 - 9</td>
</tr>
<tr>
<td>10 - 14</td>
</tr>
<tr>
<td>15 - 19</td>
</tr>
<tr>
<td>20 - 29</td>
</tr>
<tr>
<td>30 - 59</td>
</tr>
<tr>
<td>60 - 119</td>
</tr>
<tr>
<td>120 - 179</td>
</tr>
<tr>
<td>180 - 239</td>
</tr>
<tr>
<td>240 - 479</td>
</tr>
<tr>
<td>≥480</td>
</tr>
</tbody>
</table>

Frequency: 1.5 for each day on which the patient had had pain in the preceding two weeks

<table>
<thead>
<tr>
<th>Stopping daily activity</th>
<th>Yes</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Night waking</th>
<th>Yes</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Epigastric tenderness</th>
<th>Yes</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
</tbody>
</table>

RESULTS
57 patients were studied, 39 male and 18 female with a mean age of 34 years and a mean length of history of 38 months (range 0.5-240). Most were from the tribes of Northern Nigeria (58%), few drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and pepper (33%).
Symptom Score: Mean 30.5 Median 30 Range 14 - 47

Macroscopic findings on endoscopy were: normal in 39 (68%), duodenitis in 5 (9%), gastritis in 5 (9%), duodenal ulcer in 6 (10.5%), gastric ulcer (prepyloric) in 1 and carcinoma of the stomach in 1. Culture was attempted in 21 (all showed Helicobacter like organisms on histology), and successful in 13. (see page 107)

On histological examination of biopsies 53/57 (93%) patients had histological gastritis and of these 46/53 (87%) were also infected with H. pylori.

Table 4: Relationship of histological gastritis to \textit{H}. \textit{pylori} (Hp) infection and diagnosis

<table>
<thead>
<tr>
<th>PATIENT GROUP</th>
<th>HISTOLOGY &amp; HELICOBACTER PYLORI STATUS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gastritis Hp +ve</td>
<td>Gastritis Hp -ve</td>
</tr>
<tr>
<td>Non-ulcer dyspepsia</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>Duodenal Ulcer</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Gastric Ulcer</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Carcinoma of Stomach</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>46(80.7%)</td>
<td>7(13%)</td>
</tr>
</tbody>
</table>

DISCUSSION

The major findings in this study are: the high incidence of non-ulcer dyspepsia (86%), and the high prevalence of gastritis (93%) and \textit{H}. \textit{pylori} infection (83%).

The proportion of patients with non-ulcer dyspepsia is much higher than found amongst dyspeptic inpatients at the teaching hospital, where, of 99 patients who had a definitive diagnosis, 60 (61%) had a duodenal ulcer and only 39% non-ulcer dyspepsia. This is probably accounted for by the fact that the in-patients were selected on the basis of the severity of their symptoms and the complications of proven peptic ulceration, although there may also have
been some over reporting of duodenal ulcers on barium meal examinations. Abebe (1983) in Ethiopia found that 63% of 1,735 patients with dyspepsia had non-ulcer dyspepsia.

There is a high prevalence of *H. pylori* infection and gastritis. *H. pylori* was present in all patients with peptic ulceration and 80% of those with non-ulcer dyspepsia. This compares with figures from Australia of 90% colonisation in duodenal ulcer, 70% in gastric ulcer and 60% in non-ulcer dyspepsia (Marshall & Warren, 1984). Gastritis was present in 47/57 (82.7%) which compares with a prevalence of 98/100 (98%) in Ethiopia (Manley, et al, 1983).

**COMMENT**

The high prevalence of *H. pylori* infection in patients with non-ulcer dyspepsia suggests that it may be important in its aetiology.
Dyspepsia occurs throughout the population of north east Nigeria accounting for 20/1,000 admissions to the University of Maiduguri Teaching Hospital and 4.1% of consultations to rural health posts. In a random sample of the rural population 26% of adult subjects had experienced dyspepsia within the preceding six months. The patients are generally young, from the northern tribes of Nigeria and have a long history.

The prospective study of these patients with dyspepsia shows that most of them (86%) have non-ulcer dyspepsia and there is a strong association with H.pylori gastritis (81%).

However before one can conclude that there is a causal relationship between H.pylori gastritis and non-ulcer dyspepsia it is important to confirm this association in a larger group of patients and to exclude the presence of H.pylori and/or gastritis in those without symptoms. Finally, one must be able to show a significant improvement in symptoms when H.pylori is cleared. These further studies make up the main body of this thesis.
CHAPTER 2

LITERATURE REVIEW
NON-ULCER DYSPEPSIA IN AFRICA
OUTLINE

1 DEFINITION

2 AN HISTORICAL PERSPECTIVE

3 EPIDEMIOLOGY

4 PRESENTATION & DEMOGRAPHY

5 CAUSE:
   DUODENITIS
   ACID
   DYSMOTILITY
   GASTROINTESTINAL POLYPEPTIDES
   ALKALINE REFLUX GASTRITIS
   GAS
   BILIARY DYSKINESIA
   PSYCHOSOCIAL FACTORS & STRESS
   ENVIRONMENTAL FACTORS & DIET
   GENETIC FACTORS
   TYPE B GASTRITIS:

   H. PYLORI:

   H. PYLORI:

6 TREATMENT

7 AFRICAN DIFFERENTIAL DIAGNOSIS:
   PARASITES
   GALLSTONES
   TROPICAL PANCREATITIS
   HIATUS HERNIA & GASTRO-OESOPHAGEAL REFLUX

8 CONCLUSION
THE DEFINITION OF NON-ULCER DYSPEPSIA

Dyspepsia is a word derived from the Greek (dys = bad, peptein = to cook or digest) and can be defined as ‘chronic pain in the epigastrium, which is episodic in nature, related to eating and leads the clinician to suspect a peptic ulcer’ (Thompson, 1984).

However due to the limited number of symptomatic responses of the upper gastrointestinal tract, many different pathologies present with these symptoms (Crean, et al., 1982). In an attempt to clarify the situation and classify the different causes of dyspepsia a committee of eminent gastroenterologists, under the chairmanship of Dr Duncan Colin-Jones (1988a) was set up. They defined non-ulcer dyspepsia as: ‘upper abdominal or retrosternal pain, discomfort, heartburn, nausea, vomiting, or other symptom considered to be referable to the proximal alimentary tract, and lasting for more than 4 weeks, unrelated to exercise, and for which no focal lesion or systemic disease can be found responsible’. They further divided dyspepsia into five groups: those with ulcer-like symptoms, those with symptoms of gastro-oesophageal reflux, those with dysmotility symptoms, those with ‘gas’ symptoms and those with ‘idiopathic dyspepsia’ that does not fit into any of these categories.

AN HISTORICAL PERSPECTIVE

'THE WEST': The Classical Period:

Dyspepsia was first noted in Greece in the fifth century BC (Talley, 1986), however it was the classical teaching of the Roman physician Galen 130-200 AD that held sway for many centuries (Hunt, 1972). This stated that food was ‘cooked’ or concocted in the stomach, the diaphragm acting as a partition to protect the heart from the resulting vapours. Dyspepsia was thought
to result from too little innate heat or too much food which 'overwhelmed and choked the heart and therefore accumulated many crude and raw humours' (Hunt, 1972).

**The Renaissance:** Unquiet meals make ill digestions.
The Comedy of Errors, William Shakespeare.

In 1547 Andrew Boore described the symptoms of gastro-oesophageal reflux after meals (Hunt, 1978) and in 1586, Marcello Donati was the first to record a case of gastric ulceration (Morton, 1983). However treatment remained largely empirical, with rest, tobacco, coffee, purgatives and wine all prescribed frequently.

**The Beginning of the Scientific Era: 18th. & 19th. Centuries**

In 1780 Spallanzani concluded that the stomach secreted a gastric juice that dissolved the food contents (1803). In 1883, William Beaumont published a classic monograph of his studies on Alexis St Martin, a patient who had sustained a gastric fistula (Beaumont, 1833). Beaumont observed duodenogastric reflux and made the first descriptions of gastric changes during emotional upset. Duodenal ulcer was described in 1746 (Morton, 1983) and in 1728, George Stahl described gastritis (Schindler, 1947).

**The 20th. Century:**

In 1897 Roux & Balthazard did the first contrast studies on humans. So came the realisation that many patients with 'typical' ulcer symptoms had no signs of an ulcer on barium meal or at operation (Rivers, 1931). The syndrome of non-ulcer dyspepsia was born (Bockus, 1963). With the invention of the gastroscope, non-ulcer dyspepsia has been diagnosed in up to half of all patients with dyspepsia.
AFRICA

Western medicine has come to Africa relatively recently, the health service in Nigeria was devoted entirely to the care of colonial staff well into this century. In the 1920’s and 1930’s reports of peptic ulceration started appearing in the medical literature from operative and post mortem studies, but there is little early data published on non-ulcer dyspepsia. This is perhaps not surprising as contrast X-rays and fibreoptic endoscopes have not been generally available in Africa. The most comprehensive work on non-ulcer dyspepsia in Africa has been carried out by Edemarian Tsegas and colleagues (1983).

EPIDEMIOLOGY

DYSPEPSIA: INCIDENCE & PREVALENCE: The "West"

Dyspepsia is a common symptom, in the United Kingdom accounting for 1 - 4% of consultations to general practitioners (Jones and Lydeard, 1989, Gear and Barnes, 1980). A large proportion of these patients are referred for specialist advice. Crean, et al, (1982) has estimated that over half of all gastroenterology referrals are for dyspepsia.

However many patients with dyspepsia do not consult their doctors (Jones and Lydeard, 1989), so these figures are inevitably an underestimate of the true prevalence within the community which random community based studies in the UK. have shown to be 25-38% (Doll et al., 1951, Weir and Backett, 1968, Jones and Lydeard, 1989). What proportion of these patients have non-ulcer dyspepsia? In 14 representative reports of patients presenting with dyspepsia since World War II between 14% and 67% have non-ulcer dyspepsia, with a mean of 45% (see Table 5).
Table 5: Proportion of dyspeptic patients without abnormalities of the upper gastrointestinal tract in studies conducted in the last 50 years.

<table>
<thead>
<tr>
<th>Investigators</th>
<th>Year</th>
<th>No. of Patients</th>
<th>% in whom no lesion was found</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jones</td>
<td>1945</td>
<td>8,985</td>
<td>47</td>
</tr>
<tr>
<td>Friedman</td>
<td>1948</td>
<td>138</td>
<td>67</td>
</tr>
<tr>
<td>Williams et al</td>
<td>1957</td>
<td>775</td>
<td>60</td>
</tr>
<tr>
<td>Krag</td>
<td>1965</td>
<td>430</td>
<td>30</td>
</tr>
<tr>
<td>Edwards &amp; Coghill</td>
<td>1968</td>
<td>424</td>
<td>52</td>
</tr>
<tr>
<td>Davis &amp; Williams</td>
<td>1968</td>
<td>1,663</td>
<td>47</td>
</tr>
<tr>
<td>Barnes et al</td>
<td>1974</td>
<td>56</td>
<td>40</td>
</tr>
<tr>
<td>Mollman et al</td>
<td>1975</td>
<td>197</td>
<td>55</td>
</tr>
<tr>
<td>Horrocks &amp; de Dombal</td>
<td>1978</td>
<td>360</td>
<td>14</td>
</tr>
<tr>
<td>Beavis et al</td>
<td>1978</td>
<td>110</td>
<td>33</td>
</tr>
<tr>
<td>Gear &amp; Barnes</td>
<td>1980</td>
<td>346</td>
<td>47</td>
</tr>
<tr>
<td>Pribe et al</td>
<td>1982</td>
<td>88</td>
<td>42</td>
</tr>
<tr>
<td>Lobo &amp; Dickenson</td>
<td>1988</td>
<td>206</td>
<td>40</td>
</tr>
<tr>
<td>Kerrigan et al</td>
<td>1990</td>
<td>1,545</td>
<td>40</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>45%**</td>
</tr>
</tbody>
</table>

** For the studies since 1975 the mean is 36%.

Africa

It is a reasonable conclusion that while peptic ulcer appears to be rare in many parts of Africa, convincing proof of this has been nowhere forthcoming.

Alan B. Raper, 1958

In Africa it is difficult to calculate the prevalence of non-ulcer dyspepsia due to a scarcity of diagnostic facilities, and an almost total absence of reliable population statistics. Further, African hospitals tend to be swamped by patients with serious disease, often managed by a limited number of doctors with inadequate facilities, so that the diagnosis of a benign disease such as non-ulcer dyspepsia has not been a major priority.

Most reports in the literature deal with peptic ulceration and Tunstall & Tovey (1975) in a comprehensive review delineate areas where
Peptic ulceration is common (coastal areas of West Africa and the Nile/Congo watershed) and areas of low prevalence (northern savannah of West Africa).

Dyspepsia accounted for 3.7% of two and a quarter million patients presenting to primary care health posts throughout Ethiopia (Mengesha, 1983) and 6.8% of admissions to various hospitals in Addis Ababa (Lester and Tsega, 1976).

In Africa the only random, population based study of dyspepsia is that done as part of the pilot study, in which a six month prevalence of dyspepsia of 26% amongst adults was found, remarkably similar to that found in the 'West'. What proportion of these patients have non-ulcer dyspepsia?

In those patients investigated for dyspepsia in Africa a higher proportion have non-ulcer dyspepsia than their Western counterparts, with a mean of 78%, more than double the figure for the 'West' (see table 6). This may be related to the age distribution of the population in Africa. Fifty percent of the population is under 20 years of age so that the mean age of the patients in these series is considerably younger than in comparable series from the 'West' and serious upper gastrointestinal pathology is uncommon in this age group.

**Table 6: Incidence of Non-ulcer Dyspepsia in patients presenting with dyspepsia in Africa**

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Number of patients</th>
<th>% with non-ulcer dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Umerah, et al.</td>
<td>1978</td>
<td>568</td>
<td>70</td>
</tr>
<tr>
<td>Stahel, et al.</td>
<td>1981</td>
<td>79</td>
<td>90</td>
</tr>
<tr>
<td>Abebe</td>
<td>1983</td>
<td>1,735</td>
<td>65</td>
</tr>
<tr>
<td>Holcombe, et al.</td>
<td>1990</td>
<td>57</td>
<td>86</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>78</td>
</tr>
</tbody>
</table>
PRESENTATION AND BASIC DEMOGRAPHY
The symptoms of duodenal ulcer in many cases are perfectly characteristic and admit of an unhesitating diagnosis.
Lord B.G.A. Moynihan, 1905.

With these words, written in the Lancet, Lord Moynihan ushered in the new century and the new disease of duodenal ulcer. Unfortunately this statement, made before the diagnosis of non-ulcer dyspepsia was appreciated, has not been borne out by subsequent experience.

De Luca, et al (1981) found that up to 40% of patients with classical symptoms of duodenal ulcer did not have an identifiable ulcer crater. Non-ulcer dyspepsia can only be diagnosed on the basis of investigation, and this is underlined by Mengitsu (1983) in a study from Ethiopia. In 60 patients with endoscopically proven duodenal ulcer the correct diagnosis was made on the basis of symptomatology in only 40%. Indeed, my own experience in Maiduguri is that it is the patients with ‘typical ulcer symptoms’ that have non-ulcer dyspepsia, while those with atypical symptoms, not infrequently have an ulcer.

PROGNOSIS
Non-ulcer dyspepsia is a benign disease and there is usually an improvement in the amount and frequency of pain with time. After 5 years follow up Bonnevie (1982) found that of 85 patients, one third had no pain at all, one third had pain which did not infringe the working capacity and one third had pain which interfered with their working capacity at least two weeks in the year, while 11% of patients had no pain at all during the 5 years of the follow up. A proportion of patients will subsequently develop a peptic ulcer, figures of 3 - 40% are recorded in the literature (Gregory, et al, 1972, Krag, 1969) and approximately 7% will be given a different definitive diagnosis (Bonnevie, 1982).
INTRODUCTION

The search for the cause of non-ulcer dyspepsia has been long and inconclusive. In a recent review Talley and Phillips, (1988) consider 14 possible causes. There are several problems; many researchers have not adequately defined non-ulcer dyspepsia, while the populations under study have not always been comparable; some have been community based, others hospital based. Non-ulcer dyspepsia is a very common problem with a benign course, it is difficult therefore to condone extensive investigation both because of the cost, and of the inconvenience to the patient. Finally there is a tendency to look at the aetiology of disease rather simplistically, we search for the cause of non-ulcer dyspepsia when more probably there are several aetiological factors, all of which work together.

The following section reviews the published literature on the cause of non-ulcer dyspepsia with particular emphasis on Africa and the possible role of H. pylori.

DUODENITIS

Historical Perspective

Duodenitis was described by Baudin in 1837 and in 1921 Judd observed duodenal inflammation without signs of past or present ulceration. Whitehead (1982) gives a good review of the diagnostic criteria for histological duodenitis.

Prevalence

Less than 10% of healthy volunteers have duodenitis (Kreuning, 1978). While in patients with dyspepsia the prevalence varies from 31 of 1800 (1.7%) biopsies (Cheli, et al, 1973) to 42 of 100 patients (42%) (Greenlaw, et al, 1980). It is generally accepted that duodenitis occurs in less than 20% of
patients with dyspepsia.

There has been much discussion as to whether or not duodenitis is part of the peptic ulcer diathesis. Venables, et al (1980) found that 93% of their patients with endoscopic duodenitis had evidence of past or present peptic ulcer. Mackinnon, et al, (1982), found a significant improvement in symptoms and duodenitis on treatment with cimetidine. Joffe (1982) and Myren (1982) have found high levels of acid output in patients with duodenitis, and 6 of 14 patients with duodenitis reported by Thompson, et al, (1977) developed a duodenal ulcer.

**Comment** (see figure 10)

The evidence suggests that duodenitis is part of the duodenal ulcer diathesis rather than a separate disease and it may represent both the production and healing phases of duodenal ulceration. It is likely that in a small proportion of patients with non-ulcer dyspepsia this is accounted for by duodenitis.

Fig.10. Schematic representation of duodenitis as part of pathophysiological spectrum of the duodenal ulcer diathesis (Joffe, et al, 1978).
ACID

Introduction

A strong and recurring theory of the aetiology of non-ulcer dyspepsia has been that it is caused by excess acid (Lagarde & Spiro, 1984). There are three questions, the answers to which help us in this problem: Is gastric acid secretion abnormal in non-ulcer dyspepsia? Does acid bathing the mucosa cause symptoms? Does elimination or reduction in acid output lead to the resolution of symptoms?

Gastric Acid Secretion in Non-ulcer Dyspepsia

Most studies have failed to show any consistent difference in basal acid output or peak acid output, between patients with non-ulcer dyspepsia and normal controls (Mollman, et al, 1976). Tsega, et al (1983) compared basal and maximal acid outputs in 67 patients with non-ulcer dyspepsia and 38 normal controls in Ethiopia and did not find a significant difference between the two groups.

Acid & Symptoms

The only evidence that acid causes pain in non-ulcer dyspepsia comes from two uncontrolled studies. Joffe and Primrose (1983) elicited pain in patients with duodenitis, while Moraes-Filho (1974) found a significant correlation between histologically proven gastritis and pain when acid was infused.

Acid Suppression

The symptomatic improvement when acid is suppressed has been unconvincing (see table 7) Olubuyide, et al (1986) in a double blind trial comparing acid suppression using ranitidine with placebo in Nigerian patients with non-ulcer dyspepsia did not find any significant difference between the two treatment groups.
Table 7: Results of Acid Suppression in Patients with Non-ulcer Dyspepsia

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Nos</th>
<th>Agent</th>
<th>Comparison</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delattre, et al</td>
<td>1985</td>
<td>414</td>
<td>Cimetidine</td>
<td>Placebo</td>
<td>Cimetidine superior</td>
</tr>
<tr>
<td>Kelbaek, et al</td>
<td>1985</td>
<td>50</td>
<td>Cimetidine</td>
<td>Placebo</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Kleveland, et al</td>
<td>1985</td>
<td>27</td>
<td>Cimetidine</td>
<td>Placebo</td>
<td>Pts. with heartburn responded to Cimetidine</td>
</tr>
<tr>
<td>Casiraghi, et al</td>
<td>1986</td>
<td>104</td>
<td>Cimetidine</td>
<td>Antacid</td>
<td>Cimetidine superior</td>
</tr>
<tr>
<td>Lance, et al</td>
<td>1986</td>
<td>60</td>
<td>Cimetidine</td>
<td>Placebo</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Nyren, et al</td>
<td>1986</td>
<td>159</td>
<td>Cimetidine</td>
<td>Placebo &amp; Antacids</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Saunders, et al</td>
<td>1986</td>
<td>251</td>
<td>Ranitidine</td>
<td>Placebo</td>
<td>Ranitidine superior</td>
</tr>
<tr>
<td>Gotthard, et al</td>
<td>1988</td>
<td>228</td>
<td>Cimetidine</td>
<td>Placebo &amp; Antacids</td>
<td>Cimetidine superior</td>
</tr>
</tbody>
</table>

**Comment**

On the available evidence acid does not play a major role in the aetiology of non-ulcer dyspepsia.

**DYSMOTILITY**

**Introduction**

Disordered motility of the upper gastrointestinal tract has been implicated in the cause of non-ulcer dyspepsia and Colin-Jones (1988a) has described the symptoms of ‘dysmotility like’ dyspepsia.

**Dysmotility**

Where abnormalities of motility have been demonstrated, they have occurred in specific groups of patients, mainly those with prominent nausea (Malagelada and Stanghellini, 1985, Geldof, et al, 1986) or in those with other pathologies eg. anorexia nervosa, diabetes or postgastrectomy (Azpiroz &
Medication

Metoclopramide, cisapride and domperidone modify gastric motility and have all been used in the treatment of non-ulcer dyspepsia (Johnson, 1971, Englert, 1979, Rosch, 1987). Most studies have found these agents superior to placebo, however these trials have included many patients with organic disease, and, even in those patients in whom no organic cause for their symptoms was known, the main complaints were nausea and postprandial bloating, putting them firmly into the category of ‘dysmotility type dyspepsia’ as defined by the dyspepsia working party (Colin-Jones, 1988a).

Comment

Studies in which patients with known pathology and irritable bowel syndrome have been excluded are lacking. There is little evidence that disorders of motility cause non-ulcer dyspepsia.

GASTROINTESTINAL POLYPEPTIDES

An attractive speculation is that functional disturbances of the upper gastrointestinal tract are mediated hormonally. However no consistent abnormality in gastrointestinal polypeptides levels has been demonstrated in patients with non-ulcer dyspepsia. Watson and colleagues (1986) found no differences in levels of insulin, gastrin, gastric inhibitory polypeptide, pancreatic polypeptide or neurotensin between symptomatic patients with flatulent dyspepsia and controls although Nyren et al (1986b) did find a small rise in basal levels of gastrin in patients with non-ulcer dyspepsia.

The role of gastrointestinal polypeptides remains unclear.
ALKALINE REFLUX GASTRITIS

Introduction

Post operative alkaline reflux gastritis characterised by epigastric pain and bile vomiting was first described by Billroth in 1885, and a good review of the syndrome is given by Ritchie (1984). However the relevance of reflux in the unoperated stomach is unclear.

Cheng, et al (1969) have demonstrated that exposure of the proximal gastric mucosa to intestinal content can cause gastritis. Patients putatively suffering from the ‘syndrome’ developed ‘typical’ symptoms when challenged with an intragastric solution of concentrated NaOH, while control patients did not (Warshaw, 1981), findings confirmed by Meshkinpour, (1980). Hoare, et al, 1978, and Ritchie, 1980, have reported the improvement of symptoms when reflux was eliminated. However reflux is no more frequent in patients with non-ulcer dyspepsia than asymptomatic controls (Hughes, et al, 1982, Niemela, 1985), although Tolin, et al (1979) have suggested there may be a quantitative difference.

Comment

The evidence for a major role in the aetiology of non-ulcer dyspepsia remains unconvincing.
**GAS**

**Basic Physiology: Source & Volume**

Gas can either be swallowed or generated within the gut by metabolism, mainly in the colon (Levitt & Bond, 1970). Washout techniques using inert gas (Lasser, et al, 1975), suggest that the gut normally contains approximately 100mls of gas (Mendeloff, 1976).

**Clinical Correlation**

'When I thought I was full of gas there was no sign of it in the bowel, and when I was comfortable the roentograms sometimes showed the splenic flexure to be markedly distended'.


Distension of the bowel can cause pain, as first demonstrated by Hurst in 1911. Moriaty and Dawson (1982) produced pain by balloon dilatation of the ileum, jejunum, duodenum and oesophagus. However using a washout technique with intestinal infusion of inert gas Lasser, et al (1975) found that the volume of gas in the intestinal tract of 12 patients complaining of 'excess gas' (176 mls.) did not differ significantly from that of 10 controls (199 mls.) although patients did complain of pain on infusion of relatively small volumes of gas.

**Comment**

Most of this work has been on patients with irritable bowel syndrome, and it seems that if these were excluded very few of those remaining with non-ulcer dyspepsia would have a 'gas problem'.
BILIARY DYSKINESIA

Introduction

Biliary dyskinesia has been defined as a motility disorder of the biliary tract that causes an impedance to the flow of bile into the duodenum. Patients present with typical biliary tract pain and in addition have an elevated alkaline phosphatase and/or bilirubin, a dilated common bile duct and delayed drainage of contrast from the common bile duct on ERCP, in the absence of any other biliary pathology (Lempinen, 1985).

Diagnosis


Treatment

Sphincterotomy, either operative or endoscopic has been used to treat this syndrome, the results have, however, been very variable. This may be due to false positive diagnosis or to inadequate treatment as in some patients the sphincter muscle extends as far as 30 mm from the papilla (Lempinen, 1985).

Comment

Biliary dyskinesia is described principally in those who have undergone cholecystectomy and is unlikely to be the cause of dyspepsia in all but a very small proportion, if any, of those with non-ulcer dyspepsia. Conceivably, biliary dyskinesia could cause pain in those who have not undergone cholecystectomy, but even then, the pain is biliary and using the strict diagnosis of non-ulcer dyspepsia, as defined above, most of these patients would be excluded on clinical grounds.
PSYCHOSOCIAL FACTORS AND STRESS

‘It is scarcely in doubt that significant life events or emotional conflicts will provoke gastrointestinal pain’.


Introduction

Despite this bold statement by Blendis et al (1978) the relevance of personality and stress to non-ulcer dyspepsia is far from clear.

Personality: Beaumont (1833) noted the effect of the emotions on the gastric mucosa. Hill and Blendis (1967) reported a high neuroticism score in patients with non-ulcer dyspepsia, but without controls. Viskum (1977) also found increased neurosis in dyspeptics, but in highly selected inpatients. Talley et al (1986) found dyspeptics to be more anxious and depressed than controls, but the difference was small. Meanwhile Jorsensen, et al (1986) have suggested that patients with non-ulcer dyspepsia have a lowered pain threshold.

Stress: Hill & Blendis, (1967) and Craig & Brown, (1984), have reported an increase in stress that preceded the diagnosis of non-ulcer dyspepsia. However Talley & Piper (1986) in a well designed study of 68 patients with non-ulcer dyspepsia found no excess stress compared with 68 matched community controls, a finding confirmed by Gomez and Dalley (1977).

Comment

Contrary to popular belief, the evidence for stress, emotion or personality trait having a role in non-ulcer dyspepsia is so thin as to be almost non-existent. At best, Talley, et al, (1986) have demonstrated patients with non-ulcer dyspepsia to be slightly more anxious, depressed and neurotic than the general population.
ENVIRONMENTAL FACTORS AND DIET

Introduction

A number of environmental and dietary factors have been implicated in the aetiology of non-ulcer dyspepsia, and patients are commonly advised to avoid exposure to cigarette smoke, alcohol, analgesics and coffee, but there is little evidence to support this advice.

Smoking & Alcohol: Smoking is less common in patients with non-ulcer dyspepsia than those with ulcers (Tibblin, 1985, Heatley and Rathbone, 1987). Talley et al, (1988) in a case control study of patients with well defined dyspepsia did not find smoking or alcohol to be a risk factor, a finding confirmed by others (Roberts, 1972).

Analgesics: Non-steroidal anti-inflammatory drugs and aspirin have been implicated in the genesis of dyspepsia (Thompson, 1984). Aspirin does induce acute dyspepsia more often than placebo (Aspirin Myocardial Infarction Study Research Group, 1980), but in the only case control study, in 113 patients with chronic dyspepsia an association with aspirin ingestion was not found (Talley et al, 1988).

Coffee: Coffee can promote gastro-oesophageal reflux (Cohen, 1980) and thereby cause heartburn, it may also act as a direct irritant (Price, et al, 1978). However in the only controlled study Talley (1988 et al.), in which patients with gastro-oesophageal reflux were excluded, coffee and tea were not associated with non-ulcer dyspepsia.

Food: Many patients report that their symptoms are precipitated by particular foods (Friedlander, 1959) and fatty foods are commonly implicated (Taggart and Billington, 1966). However in a double blind study Taggart and Billington (1966) showed that patients did not have dyspepsia when they ate...
disguised food. There is no evidence that edentulous patients, because of inability to chew, have more dyspepsia (Sircus & Prestcott, 1985).

**GENETIC FACTORS**

Once again the situation is unclear and the topic has not really been adequately addressed. Family clusters have been reported (Hill and Blendis, 1967 & Viskum, 1977) but these studies included patients with irritable bowel syndrome and in any case could be accounted for by hereditary or environmental factors. The available data does not support a major role (if any) for genetics.
**TYPE B ANTRAL GASTRITIS**

**Historical Perspective**

In 1728, George Stahel was the first to describe gastritis (Schindler, 1947) and in 1870 Fenwick described the histological changes of gastric atrophy in a post mortem study of a patient with pernicious anaemia. The gastric atrophy of pernicious anaemia and the gastritis accompanying gastric ulcer and gastric cancer were differentiated by Magnus in 1937, using ‘Swiss roll’ preparations of large areas of the stomach.

In 1973 Strickland and Mackay distinguished between type A and type B gastritis and in 1983 Warren and Marshall ‘rediscovered’ curved bacilli on the gastric epithelium associated with Type B antral gastritis. This represents the latest significant discovery providing for the first time firm evidence of an aetiological agent for Type B gastritis (Wyatt & Dixon, 1988).

**Type B Gastritis**

In 1973 Strickland and Mackay divided chronic non-specific gastritis into two distinct clinicopathological patterns. One, (Type A), the autoimmune gastritis which leads to pernicious anaemia, mainly affects body mucosa and is associated with hypochlorhydria and the presence in the serum of anti-parietal cell antibodies. The other, (Type B gastritis), is found predominantly in the antrum and is associated with hyperchlorhydria and peptic ulceration.

With the discovery of *H. pylori* and the recognition of its role in the aetiology of gastritis (vide infra), a new classification of gastritis has been devised. This new classification, the Sydney system, covers both histological and endoscopic findings and allows classification of aetiology, topography, morphology and severity (see table 8) (Misiewicz, et al, 1990)
Table 8.
The Sydney System

Gastritis in Hookworm Disease and Tropical Sprue
Comment should be made on two papers by Floch and Thomassen (Floch & Thomassen, 1963, Floch, et al, 1963). In the first study of 10 patients with hookworm disease, they found that 7 (70%) patients had gastritis. In the second study of 21 patients with tropical sprue 14 (67%), had gastritis. In each study, follow up after treatment showed no difference in the prevalence or severity of the gastritis. The authors suggest that these diseases may cause gastritis. Both studies are basically flawed by the absence of any controls and other studies from the ‘Developing World’ have since shown a prevalence of gastritis not significantly different from that found by Floch & Thomassen (1963).

The Epidemiology of Gastritis
In 1955 Joske, et al, from Australia reported a series of 1000 biopsies performed in 623 patients, their results are summarised in figure 11.

Fig.11. Patients with gastritis according to age & type of gastritis.
In 1972 Kimura studied 570 asymptomatic Japanese patients who did not have discrete upper gastrointestinal lesions seen on endoscopy or upper gastrointestinal radiological studies. He clearly demonstrated three features that have been supported by most other studies (see table 9): a) gastritis as determined histologically increases in frequency with increasing age, b) gastritis increases progressively from the cardio-oesophageal junction to the pylorus and c) at similar levels the lesser curvature has more severe grades of gastritis than the greater curvature. This study clearly demonstrated the value of age matched controls and a precise biopsy site.

**Table 9: Age Matched Prevalence of Gastritis**

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Subjects</th>
<th>Age</th>
<th>No</th>
<th>Normal</th>
<th>Gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SG  AG</td>
</tr>
<tr>
<td>Joske, et al.</td>
<td>1955</td>
<td>Patients</td>
<td>21-30</td>
<td>79</td>
<td>51%</td>
<td>38% 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61-70</td>
<td>177</td>
<td>19%</td>
<td>38% 44%</td>
</tr>
<tr>
<td>Siurala, et al.</td>
<td>1968</td>
<td>Random</td>
<td>21-30</td>
<td>31</td>
<td>71%</td>
<td>19% 10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61-65</td>
<td>15</td>
<td>13%</td>
<td>27% 54%</td>
</tr>
<tr>
<td>Kimura</td>
<td>1972</td>
<td>Assymp.</td>
<td>21-30</td>
<td>570</td>
<td>45%</td>
<td>15% 38%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>51-60</td>
<td></td>
<td>7%</td>
<td>7% 86%</td>
</tr>
<tr>
<td>Kreuning, et al.</td>
<td>1978</td>
<td>Assymp.</td>
<td>20-58</td>
<td>50</td>
<td>64%</td>
<td>8% 28%</td>
</tr>
<tr>
<td>Ihamaki, et al.</td>
<td>1979</td>
<td>Assymp.</td>
<td>15-30</td>
<td>77</td>
<td>62%</td>
<td>15% 11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65+</td>
<td>56</td>
<td>18%</td>
<td>39% 43%</td>
</tr>
<tr>
<td>Barthel, et al</td>
<td>1988</td>
<td>Assymp.</td>
<td>23-50</td>
<td>20</td>
<td>80%</td>
<td>10% 10%</td>
</tr>
<tr>
<td>Dooley, et al</td>
<td>1989</td>
<td>Assymp.</td>
<td>21-30</td>
<td>113</td>
<td>80%</td>
<td>20% 48%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61-70</td>
<td></td>
<td>52%</td>
<td>21% 22%</td>
</tr>
<tr>
<td>Approximate Means</td>
<td></td>
<td></td>
<td>21-30</td>
<td></td>
<td>59%</td>
<td>26% 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>61-70</td>
<td></td>
<td>21%</td>
<td>22% 57%</td>
</tr>
</tbody>
</table>

No: number, SG: superficial gastritis, AG: atrophic gastritis
Africa

Table 10: Prevalence of Gastritis in Asymptomatic Subjects in the Developing World

<table>
<thead>
<tr>
<th>Study</th>
<th>Date</th>
<th>Subjects</th>
<th>Mean Age</th>
<th>No</th>
<th>Normal</th>
<th>Gastritis SG</th>
<th>AG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Russel, et al (Pakistan)</td>
<td>1966</td>
<td>Assymp.</td>
<td>17</td>
<td>49</td>
<td>4%</td>
<td>96%</td>
<td></td>
</tr>
<tr>
<td>Stahel, et al (Liberia)</td>
<td>1981</td>
<td>Assymp</td>
<td>30</td>
<td>15</td>
<td>67%</td>
<td>20% 13%</td>
<td></td>
</tr>
<tr>
<td>Tsega, et al (Ethiopia)</td>
<td>1983а</td>
<td>Assymp</td>
<td>31</td>
<td>71</td>
<td>0%</td>
<td>69% 31%</td>
<td></td>
</tr>
<tr>
<td>Lachlan, et al (Kenya)</td>
<td>1988</td>
<td>Assymp</td>
<td>22</td>
<td>14</td>
<td>7%</td>
<td>93%</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td></td>
<td>25</td>
<td></td>
<td>4%</td>
<td>96%</td>
<td></td>
</tr>
</tbody>
</table>

No: number, SG: superficial gastritis, AG: atrophic gastritis

These reports from Africa (see above), with the exception of the small study by Stahel (1981) show an extraordinarily high prevalence of histological gastritis.

Natural History of Gastritis

In a series of remarkable studies Siurala and his colleagues, have, since 1952, followed a large group of asymptomatic subjects who did not have pernicious anaemia, ulcers or dyspepsia. Their 30 to 34 year follow up was reported in 1985 (Ihamaki, 1985). The original material collected in 1950-51 consisted of 377 outpatients, of whom 168 had normal mucosa, 93 superficial and 116 atrophic gastritis in the body mucosa. They were examined by gastroscopy, multiple 'blind' suction biopsy, X-ray examination, and submaximal histamine test. The subjects were re-examined at 5 to 8 year intervals. Of the 179 subjects alive in 1983-4, 129 were re-examined.

Results

During the whole period of the study in the body mucosa there was a trend for the gastritis to progress, although this progression slowed. In
the antrum there seems to be a clear trend towards regression in old age. In a number of patients who had both antral and body gastritis the antral gastritis resolved, leaving the body gastritis only.

**Comment**

Despite the general trend in this study towards the formation of new cases of gastritis and progression of existing ones, there were in 1984 twenty one patients, with a mean age of 68 years, who after 34 years retained morphologically a completely normal mucosa in the antrum and body.

**Clinicopathological Correlations**

**Symptoms**

Does gastritis cause epigastric pain and non-ulcer dyspepsia?

The prevalence of gastritis in patients with non-ulcer dyspepsia ('Western' population) varies from 45-72% (Rokkas, et al, 1987, Loffeld, et al, 1988, Gad, et al, 1989) and is slightly higher than in controls. Siurala et al (1953) and Strickland & Mackay (1973) both correlated symptoms with gastritis, although in a further study Siurala et al (1968) did not find any difference in the prevalence of gastritis between those with and without symptoms, a finding confirmed by Oddson et al (1977). In a study of 241 patients with a variety of upper gastrointestinal symptoms there was no histological gastritis in 24% of symptomatic patients (Rao, et al, 1975).

**Africa**

Stahel et al, (1981) in a study of 79 patients presenting with epigastric pain and 15 controls, found a statistically higher prevalence of gastritis in those with symptoms (72%) compared to controls (33%). On the other hand Tsega (1983b) in a study of 106 symptomatic patients (90 with non-ulcer dyspepsia and 16 with duodenal ulcer) and 71 asymptomatic controls, found no difference in the prevalence of gastritis between the two groups.
Comment

The published evidence for an association between gastritis and non-ulcer dyspepsia is conflicting and confusing. There is no convincing evidence that gastritis causes symptoms.
HELIcobacter pylori
Fig. 12. Scanning electron micrograph of *H. pylori*.

(Dr. A. Curry, PHLS, Manchester.)
Fig.13. Transmission electron micrograph of *H. pylori*.

(Dr. A. Curry, PHLS, Manchester.)
History

Gastric Spiral Organisms: Early Work

Gastric spiral bacteria were observed in dogs as long ago as 1893 (Bizzozero). In 1939 Doenges showed them to be present in 43% of 242 stomachs at post mortem and Freedberg and Barron (1940) observed bacteria in 35 partial gastrectomy specimens. In 1954 Palmer examined a series of 1000 suction biopsies of the gastric mucosa and did not find any spirochaetes, this was probably due to poor staining and a blind biopsy technique. Whatever the reason this negative result in such a large series of patients effectively curtailed further research into gastric spiral organisms for the next 20 years.

Gastric Urease

The enzyme urease was first noted in the gastric mucosa in 1924 (Luck & Seth), this was thought for many years to be intrinsic to the mucosal cells, until Delluva, et al (1968) demonstrated the absence of urease in germ free animals thus proving that urease was not present in mammalian tissue but was solely the product of bacterial metabolism.

Discovery

Interest in spiral gastric organisms was rekindled in 1975 by Steer and Colin-Jones (1975) who wondered if bacteria might be involved in the aetiology of peptic ulceration by damaging mucous and predisposing to penetration of acid (Colin-Jones, 1988b). They studied the histological effects of carbenoxolone on the gastric mucosa of 50 patients treated for gastric ulcers. They observed that gram-negative bacteria were present on the gastric mucosa of 80% of their patients and that the bacteria did not disappear when the ulcers healed.

In Australia, Warren a histopathologist observed what he termed ‘Campylobacter-like organisms’ on gastric antral mucosa in association with
active chronic gastritis. Marshall and Warren began a prospective study in 100 consecutive patients who were biopsied and the biopsy findings correlated with the clinical and endoscopic data. During that study, a gram-negative, microaerophilic, catalase-positive bacterium was isolated.

In 1984 Langenberg, et al first reported that \textit{H. pylori} produced large amounts of urease, the source of gastric urease had finally been found.

\textit{Ultrastructure: External Appearance and General Description} \\
(\textit{Jones & Curry, 1989})

The 'usual' appearance of \textit{H. pylori} is that of a sinusoidal organism, ranging from 2 to 6.5\textmu m long and from one pole originate several sheathed flagellar filaments (see figures 12 & 13).

\textit{Helicobacter pylori and its Environment}

The localization of \textit{H. pylori} is limited to cells derived from gastric type mucosa (Bode, et al, 1988, Goodwin, et al, 1986) and it is most frequently found in the 'grooves' at the junction of individual epithelial cells (Steer, 1984).

\textit{Microbiology}

\textit{H. pylori} is found beneath the surface mucous layer in the gastric antrum (Quigley and Turnberg, 1987) and is best obtained from mucosal biopsies of the gastric antrum (Anderson, et al, 1987a). Many different liquid transport media have been advocated, but few formal comparisons have been made between these, the key to success is probably rapid transport from patient to the laboratory for culture (Glupczynski, et al, 1988). \textit{H. pylori} grows best in a microaerobic atmosphere of 5% O2 with 5-10% CO2 (Goodwin, et al, 1985).

The gastric biopsy specimen should be rubbed a number of times on to the media (Humphreys & O Morain, 1988). A variety of basal media with agar and added blood have been used for the isolation of \textit{H. pylori} from clinical
specimens and give comparable results (Goodwin, et al, 1985). Most workers have used selective media eg. Skirrows medium containing vancomycin, trimethoprim and polymixin B. Plates should be incubated at 30-40°C (Tompkins, 1989). Small, shiny, grey, translucent colonies are usually present at 48 hours (Humphreys & O Morain, 1988). Cultures can be identified by direct Gram’s stain of the colonies, and tests for the presence of catalase, oxidase and urease are positive (Humphreys & O’Morain, 1988).

Detection

Histology

Histology provides a reliable method for detection of \textit{H. pylori}. The Warthin-Starry silver stain was used by Warren and Marshall in their original work (Warren & Marshall, 1983), but other simpler stains are equally effective. Giemsa, haematoxylin and eosin, Giemenez and acridine orange have been successfully used (Peterson, et al, 1988).

Specificity & Sensitivity

None of the stains described above is specific for \textit{H. pylori}, but rather, demonstrate the characteristic appearance of the organism which allows \textit{H. pylori} to be recognized.

In a study of multiple gastric biopsies from 50 patients Wyatt et al (1988a) found that both gastritis and \textit{H. pylori} were diffuse in the antrum and conclude that two antral biopsies should be sufficient to avoid sampling error and establish \textit{H. pylori} status.

For comparison with other techniques see on.
**Serology: Antibody Response**


**Antigenic Specificity of anti-*Helicobacter pylori* Antibodies**

No single protein antigen has been detected which consistently reacts with all the positive sera investigated and positive sera react with a number of different proteins of different molecular weights (Jones, et al, 1986, Von Wulffen, et al, 1988). The ideal antigen has not been found and both whole cell sonicates and partly purified antigens are used (Newell & Rathbone, 1989)(see pg 118 for further discussion).

**Detection of *H. pylori* Antibodies**

The most commonly used technique for serodiagnosis is the enzyme-linked immunosorbant assay (ELISA) (Newell & Rathbone, 1989). This technique is quick, cheap, simple and reproducible (see appendix for details page 152).

**Antigenic Cross-reactivity with other Bacteria:** Some of the surface antigens of *H. pylori*, in particular the flagella proteins, share epitopes with some of the Campylobacter species (Newell, 1986). Jones, et al (1986) suggested screening for anti-C.jejuni as well as anti-*H. pylori* antibodies, and this may be particularly important in the 'Developing World' where C.jejuni infection is common (Newell & Stacey, 1989).
Comment

The measurement of circulating antibodies to \textit{H.pylori} using an enzyme linked immunosorbant assay provides a simple, reliable and non-invasive means of diagnosing \textit{H.pylori} infection, with a sensitivity of 95% and specificity of 90\%(Newell & Rathbone, 1989). For comparison with other methods of diagnosis see below.

Detection related to Urease Production

The production of urease by \textit{H.pylori} provides the basis for detection of \textit{H.pylori} by two other methods.

\textit{The Biopsy Urease Test:} detects preformed urease in gastric biopsies by means of an indicator colour change (McNulty, 1989). This test, the rapid urease test, is fast with a sensitivity of 89\% (Vaira, et al, 1988b) to 98\% (Marshall & Surveyor, 1987) and a specificity of 99\% (McNulty, 1989) to 100\% (Marshall, et al, 1987a).

\textit{The Carbon Urea Breath Tests:} are non-invasive tests which detect the presence of carbon 13 or carbon 14 carbon dioxide formed by the action of \textit{H.pylori} produced gastric urease on a labelled test meal (Weil & Bell, 1989, Graham, et al, 1987).

Choice of Method

Introduction

These tests can be divided into two major groups; those which do and those which do not require endoscopy; apart from this, each individual test has its own advantages and disadvantages.

Epidemiology

At the present time the preferred technique is serology. It is easy to obtain several microlitres of blood, very little technical backup is needed and the ELISA is adapted to screen a large number of samples (Megraud, 1988).
The cost and complexity of the breath tests limit their usefulness particularly in the ‘Developing World’.

**Clinical: Screening**

The pathological role of *H. pylori* is still unclear, however the presence of *H. pylori* does identify a ‘high risk’ group and would include the majority of patients with peptic ulceration and gastric cancer (Newell & Stacey, 1989). Serology is the method of choice of screening for this high risk group.

**Diagnosis**

Very often there will be a clinical indication for upper gastrointestinal endoscopy, during this procedure biopsies can be taken for histological diagnosis of *H. pylori* infection. If the biopsies are also cultured the antibiotic sensitivity of the organism can be tested.

**Treatment Surveillance**

In some patients repeat endoscopy will be required eg. to check for the healing of a gastric ulcer, in which case any of the biopsy methods of diagnosis are suitable. However in those in whom further endoscopy is not indicated the C13 or C14 urea breath test, gives an accurate picture of current infection and reflects the results of treatment.
**The Prevalence of Helicobacter Pylori in the Normal Population**

**Introduction**

Crucial to any consideration of the possible pathological role of *H. pylori* is a knowledge of the prevalence of infection in the normal population (see table 11 & figure 14).

**Table 11: Gastritis and *H. pylori* infection in the Normal Population: Endoscopic Studies**

<table>
<thead>
<tr>
<th>Author</th>
<th>No.</th>
<th>Age</th>
<th>Gastritis</th>
<th><em>H. pylori</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Barthel, et al, 1988</td>
<td>20</td>
<td>29</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td>Dooley, et al, 1989</td>
<td>113</td>
<td></td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>Flejou, et al, 1987</td>
<td>34</td>
<td></td>
<td>41%</td>
<td>41%</td>
</tr>
<tr>
<td>Rokkas, et al, 1987a</td>
<td>15</td>
<td>24-72</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Fitzgibbons, et al, 1988</td>
<td>116</td>
<td>16-91</td>
<td>31%</td>
<td>31%</td>
</tr>
<tr>
<td>Rauws &amp; Tytgat, 1989</td>
<td>44</td>
<td>19-71</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Lachlan, et al, Kenya, 1988</td>
<td>14</td>
<td></td>
<td>93%</td>
<td>93%</td>
</tr>
</tbody>
</table>

The endoscopic studies from the ‘West’ show a prevalence of *H. pylori* infection in asymptomatic adults varying from 13-41%. Lachlan et al, (1988) in Africa found a prevalence of 93% (13/14) in healthy volunteers. These studies confirm the previously noted strong association between *H. pylori* infection and gastritis, most recording gastritis in all those who have *H. pylori* infection.

These studies are however generally small and do not show adequate distribution across age, social class, or occupational groups. In addition there is limited geographical distribution, with all except the study by Lachlan coming from the ‘The West’. Despite the criticisms these studies have demonstrated beyond doubt that *H. pylori* gastritis does occur in large numbers of asymptomatic individuals.
Serological Studies

Serological studies can be done in much larger numbers, many are randomly chosen, allow a good distribution throughout different age groups and are more readily adaptable to use in the 'Developing World'.

Two cardinal features become apparent from these studies (see table 12). Firstly, that the prevalence of infection rises with age, and secondly, that there are wide variations between different ethnic groups.

In terms of ethnic groups these studies can be divided into three categories; those from the 'West'; those from the 'Developing World' and a group of North Australian Aborigines tested by Dwyer, et al, (1988)(see Figure 15). Most studies have been done in the 'West' and here a fairly constant pattern has been established: 15-36% of the population are infected. Overlying this is the effect of age so that few children are infected (4-32% of teenagers),
there is, then, a gradual increase in the prevalence of antibody until in the sixth decade when 30-53% of the population have antibodies to \( H.pylori \).

Table 12: Antibodies to \( H.pylori \) According to Age

<table>
<thead>
<tr>
<th>Group</th>
<th>Total</th>
<th>Age groups (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0-9</td>
</tr>
<tr>
<td>Melbourne donor</td>
<td>23/154</td>
<td>NT</td>
</tr>
<tr>
<td>Dwyer, 1989</td>
<td>(15%)</td>
<td></td>
</tr>
<tr>
<td>Victoria donors</td>
<td>49/171</td>
<td>NT</td>
</tr>
<tr>
<td>Dwyer, 1989</td>
<td>(29%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(21%)</td>
<td></td>
</tr>
<tr>
<td>France, Megraud 1989</td>
<td>347/1199</td>
<td>113</td>
</tr>
<tr>
<td></td>
<td>(29%)</td>
<td></td>
</tr>
<tr>
<td>NZ donors Morris, 1986</td>
<td>175/480</td>
<td>NT</td>
</tr>
<tr>
<td></td>
<td>(36%)</td>
<td></td>
</tr>
<tr>
<td>N.Aust.Aborigines Dwyer, 1988</td>
<td>2/274</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td>(1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(50%)</td>
<td></td>
</tr>
<tr>
<td>Vietnam Megraud, 1989</td>
<td>225/365</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>(62%)</td>
<td></td>
</tr>
<tr>
<td>Ivory Coast Megraud, 1989</td>
<td>265/374</td>
<td>116</td>
</tr>
<tr>
<td></td>
<td>(71%)</td>
<td></td>
</tr>
<tr>
<td>Algeria Megraud, 1989</td>
<td>218/277</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>(79%)</td>
<td></td>
</tr>
</tbody>
</table>

NT: not tested

The figures from the 'Developing World' are less uniform. The highest figures come from the work of Megraud, et al (1989), with overall prevalence rates of 62%, 71% and 79% for Vietnam, Ivory Coast and Algeria respectively. As well as a much higher prevalence, infection is acquired at an earlier age, and by 20 years of age 47-75% are infected, at an age when Jones et al (1986), in the UK found a prevalence of only 4%. The prevalence rate rises to 78-98% by the fifth decade.
The third group of subjects who have a markedly different pattern of infection are North Australian Aborigines, tested by Dwyer, et al (1988). This group have a very low prevalence of peptic ulceration and they have the lowest prevalence of \textit{H. pylori} infection that has been reported, with only 2 of 274 (<1%) infected.

\textbf{Comment}

Any prevalence rates in disease states must be related to controls, matched for age and ethnic group, to have any meaning. In no doubt is the fact that many millions of healthy, asymptomatic individuals all over the world are infected by \textit{H. pylori}.

\textbf{Source and Spread}

The source of \textit{H. pylori} and route of spread are unknown. No natural animal host has been found for \textit{H. pylori} (Mitchell, et al, 1989). It has been suggested by Lee & Hazell, (1988), that man is the natural host for \textit{H. pylori} and, if this is true, then one must postulate that person to person spread occurs and is the most likely means of spread.

\textbf{Ingestion}


However the evidence for person to person spread under normal circumstances is limited. Berkowicz & Lee (1987) found a higher prevalence of \textit{H. pylori} infection in mental institution residents than in controls. Mitchell, et al, (1987) reported a high incidence of infection in consanguinous contacts of
children infected by \textit{H.pylori}. In contrast Jones, et al (1987) found a low incidence of infection in household contacts of 40 patients infected by \textit{H.pylori}.

\textit{Comment}

On balance the available evidence supports the theory that \textit{H.pylori} infection is acquired by person to person contact, although the exact mechanism is not known.

\textbf{Fig.15.} Prevalence of \textit{H. pylori} in representative studies from the 'West', the 'Developing World' and 'North Australian Aborigines'.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure15.png}
\caption{Prevalence of \textit{H. pylori} in representative studies from the 'West', the 'Developing World' and 'North Australian Aborigines'.}
\end{figure}
The Cause of Type B Gastritis: The Role of Helicobacter pylori

Introduction

There has been speculation for many years on the cause of chronic gastritis. Mucosal irritants; tobacco, alcohol, hot fluids and salicylates have all been implicated (Edwards & Coghill, 1966). Dinoso (1972) found that 80% of hospitalized alcoholics had chronic antral gastritis, while Chapman (1969) found a high incidence of chronic gastritis in patients taking analgesics. Whitehead (1979) implicated certain foodstuffs and Joske (1955) implicated X-irradiation in some of his patients.

In 1983 Warren and Marshall published a paper on 'Unidentified curved bacilli on gastric epithelium in chronic gastritis'. After years of groping around in the dark, the light had been turned on!

Prevalence of Helicobacter pylori in Gastritis

Following Warren and Marshall's first descriptions of H. pylori in chronic gastritis (1983) there have been numerous studies from widely separated countries attesting to the very strong link between infection with H. pylori and gastritis (see table 13). Dixon (1989) emphasises that this association is particularly strong when the gastritis has been designated active.

Table 13: Prevalence of H. pylori infection according to presence or absence of histological gastritis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Presence of Gastritis No. Pts.</th>
<th>Hp +ve (%)</th>
<th>Normal Gastric Histology No. Pts.</th>
<th>Hp +ve (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNulty, 1984</td>
<td>62</td>
<td>76%</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td>Marshall, 1984 and Warren</td>
<td>40</td>
<td>75%</td>
<td>29</td>
<td>3%</td>
</tr>
<tr>
<td>Ho, 1986</td>
<td>122</td>
<td>97%</td>
<td>14</td>
<td>14%</td>
</tr>
<tr>
<td>von Wulffen, 1986</td>
<td>127</td>
<td>62%</td>
<td>30</td>
<td>3%</td>
</tr>
<tr>
<td>Rauws, 1989 and Tytgat</td>
<td>350</td>
<td>94%</td>
<td>19</td>
<td>7%</td>
</tr>
</tbody>
</table>
There have been six studies published from Africa (see table 14) and these all show a very high prevalence of gastritis and \textit{H.pylori} infection. 80 - 100\% of patients had gastritis, while 81 - 100\% of these patients were infected by \textit{H.pylori}.

\textbf{Table 14: Gastritis and \textit{Helicobacter pylori} infection in Africa}

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers:</td>
<td>Nigeria</td>
<td>Rwanda</td>
<td>Ghana</td>
<td>Zimbabwe</td>
<td>Kenya</td>
<td>Uganda</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>145</td>
<td>39</td>
<td>29</td>
<td>159 14*</td>
<td>47</td>
</tr>
<tr>
<td>Mean Age:</td>
<td>34yrs.</td>
<td>34.6yrs.</td>
<td>41yrs.</td>
<td></td>
<td>22yrs.</td>
<td></td>
</tr>
<tr>
<td>Gastritis:</td>
<td>53 (93%)</td>
<td>145 (100%)</td>
<td>38 (97.4%)</td>
<td>25 (86.2%)</td>
<td>125 13 (80% 92.9%)</td>
<td>40 (85%)</td>
</tr>
<tr>
<td>Gastritis: + \textit{Hp}</td>
<td>46 (81%)</td>
<td>118 (81.4%)</td>
<td>38 (97.4%)</td>
<td>24 (82.8%)</td>
<td>107 13 (67.2% 92.9%)</td>
<td>40 (85.1%)</td>
</tr>
<tr>
<td>% patients with gastritis +ve for \textit{Hp}</td>
<td>87%</td>
<td>81.4%</td>
<td>100%</td>
<td>96%</td>
<td>80% 100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

\textit{Hp}: \textit{Helicobacter pylori}. All studies on dyspeptic patients, except for one control study

* Controls

\textbf{Comment}

There is a strong association between the presence of histological gastritis and infection with \textit{H.pylori}. If the gastritis is classified according to activity the association is even more marked and if the classification of gastritis is further refined with better recognition of type B active gastritis, and the exclusion of types A and C, virtually every case of type B active gastritis is infected by \textit{H.pylori} (Dixon, 1989). This strong association, suggests that \textit{H.pylori} is the cause of type B gastritis.
Pathogenic Mechanisms

Ultrastructural features

*H. pylori* adheres to the gastric epithelium by pedestals in a very similar way to enteropathic E.coli adherence (Goodwin et al, 1986), suggesting a pathological role. Intracellular oedema occurs together with intracellular mucin depletion and microvilli are depleted or absent adjacent to bacteria. *H. pylori* have been seen in neutrophil phagocytic vacuoles (Shousa, et al, 1984). There is a correlation between the number of intraepithelial polymorphonuclear leucocytes and the number of bacteria (Steer & Colin-Jones, 1975). A number of toxins are also produced by *H. pylori*, including lipid A (Mattsby-Baltzer & Goodwin, 1988) and urease (Murakami, et al, 1987).

HUMAN INGESTION STUDIES

Introduction

In an attempt to prove that *H. pylori* was not an opportunistic organism colonising already damaged gastric mucosa Marshall and Morris (Marshall, et al, 1985, Morris & Nicholson, 1987) have both ingested cultures of *H. pylori*. In both cases *H. pylori* ingestion caused histological gastritis and in the case of Morris, infection has persisted (Morris & Nicholson, 1989) and seroconversion has occurred (Perez-Perez, et al, 1988).

Comment

These classic experiments speak for themselves. *H. pylori* infected two subjects with an entirely normal gastric mucosa and in these patients caused histological chronic active gastritis, which has persisted for almost three years in one subject.

RESULTS OF TREATMENT

McNulty et al., (1986) in an investigator blind trial compared bismuth salicylate, erythromycin ethylsuccinate, and placebo in the treatment of
\textit{H. pylori} associated gastritis in patients without peptic ulceration. \textit{H. pylori} was cleared from 15 patients, of these 13 had gastritis initially which resolved in 12. Conversely, gastritis resolved in only four of 32 patients not cleared of the organism, a highly significant difference.


\textbf{COMMENT}

The evidence for a causal role for \textit{H. pylori} in chronic, type B antral gastritis is overwhelming. There is a strong correlation between the presence of \textit{H. pylori} and chronic gastritis, particularly active chronic gastritis, ultrastructural studies have demonstrated pathogenic adherence pedestals and cellular damage in association with \textit{H. pylori}. An active immunological response has been demonstrated at the cellular level, as well as a systemic and local gastric antibody production. Ingestion of \textit{H. pylori} by subjects with previously normal gastric mucosa leads to infection by \textit{H. pylori} and the formation of active chronic gastritis, while eradication of \textit{H. pylori} leads to the resolution of gastritis.

\textit{H. pylori} causes type B, chronic antral gastritis, but does this cause symptoms, ie. non-ulcer dyspepsia?
DOES HELICOBACTER PYLORI CAUSE NON-ULCER DYSPEPSIA?

PREVALENCE

Introduction: If \( H. pylori \) causes non-ulcer dyspepsia then one would expect that the prevalence of infection amongst patients with dyspepsia would be higher than in those who are asymptomatic. It is vital however that comparison of prevalence in dyspeptics is made with controls matched for age and ethnic group.

POPULATION STUDIES

Wyatt, et al, (1988b) found an association between IgG antibodies to \( H. pylori \) and previous investigation for dyspepsia, but only in those over 40. Skoglund & Whalen (1988) found a strong positive correlation between antacid use and \( H. pylori \) colonization.

These studies suggest that there is a correlation between dyspepsia and antibodies to \( H. pylori \), however the correlation is not very striking and it must be remembered that some of those assessed by serology will either have or have had in the past a peptic ulcer, a disease which has a much stronger correlation with \( H. pylori \) infection. It is impossible to know how much this group introduces a bias to the whole sample.

ENDOSCOPIC STUDIES (see table 15)

These studies, largely from ‘Western’ populations, have demonstrated prevalence rates for \( H. pylori \) infection in patients with non-ulcer dyspepsia of between 33 and 79%. The recorded mean age varies from 40 to 56 years. However even within one country the prevalence of \( H. pylori \) infection varies from area to area in a given age group (Newell, et al, 1989). These figures are meaningless without comparison with controls matched for age and
Table 15: Frequency of H. pylori Infection determined Endoscopically in patients with Non-ulcer dyspepsia

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>No.</th>
<th>Mean Age</th>
<th>Hp +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blomberg et al, 1988</td>
<td>Sweden</td>
<td>173</td>
<td>56</td>
<td>45%</td>
</tr>
<tr>
<td>Marshall &amp; Warren, 1984</td>
<td>Australia</td>
<td>69</td>
<td>55</td>
<td>51%</td>
</tr>
<tr>
<td>Schnell &amp; Schubert, 1988</td>
<td>USA</td>
<td>30</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Rokkas et al, 1986</td>
<td>UK</td>
<td>40</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Loffeld et al, 1987</td>
<td></td>
<td>109</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>Fiocca et al, 1987</td>
<td>Italy</td>
<td>131</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>Heatley et al, 1987</td>
<td>UK</td>
<td>254</td>
<td>52%</td>
<td></td>
</tr>
</tbody>
</table>

In the studies tabled below only that by Rauws et al (1988) and that by Rokkas, et al (1987) show a significant difference in frequency of H. pylori between non-ulcer dyspepsia patients and controls. The mean age of the controls, however, was eighteen years lower than that of the patients in the study by Rauws, while the study by Rokkas et al found a low prevalence of H. pylori infection in their control group, comared to most reported studies. In the small study from Columbia Gulterrez, et al, (1988) found a higher frequency of infection in controls than in those with non-ulcer dyspepsia!

Table 16: Frequency of H. pylori infection in studies including both non-ulcer dyspepsia and normal volunteer groups

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Non-ulcer dyspepsia group</th>
<th>Normal volunteers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean Age</td>
<td>Hp +ve</td>
</tr>
<tr>
<td>Rauws et al, 1988</td>
<td>Holland</td>
<td>240</td>
<td>56</td>
</tr>
<tr>
<td>Gutierrez et al 1988</td>
<td>Colombia</td>
<td>34</td>
<td>?</td>
</tr>
<tr>
<td>Rokkas et al, 1987</td>
<td></td>
<td>55</td>
<td>39</td>
</tr>
</tbody>
</table>
PREVALENCE OF H.PYLORI IN NON-ULCER DYSPEPSIA IN AFRICA

Not surprisingly the data for Africa is even less complete. Studies have been reported from eight different countries (see table 17). In only four is the information for non-ulcer dyspepsia alone (as opposed to a mixed group of dyspeptic patients) and in only three is the mean age of the group known. All the studies show high levels of infection varying from 68% to 100%, in patient groups which are generally younger than those reported from the ‘West’.

Table 17: Non-ulcer Dyspepsia and H.pylori infection in Africa

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age:</td>
<td>34yrs.</td>
<td>35yrs.</td>
<td>41yrs.</td>
<td>46</td>
<td>24</td>
<td>127</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>H.pylori Infection</td>
<td>(80%)</td>
<td>(69%)</td>
<td>(94%)</td>
<td>(74%)</td>
<td>(83%)</td>
<td>(68%)</td>
<td>(85%)</td>
<td>(100%)</td>
</tr>
</tbody>
</table>

The first four studies are in patients with non-ulcer dyspepsia, the second four a mixed group of patients presenting for gastroscopy because of dyspepsia or epigastric pain.

It is difficult to make any meaningful comments on these figures, only Lachlan from Kenya (1988) has reported the results of any control studies and he found H.pylori infection to be more common in 13 controls (93%) than in 127 dyspeptics (68%). The prevalence of infection in patients with dyspepsia is not significantly different from that found in randomly chosen age matched groups reported by Megraud et al, (1989) for Algeria and the Ivory Coast. Again these studies do not exclude H.pylori as a possible cause of non-ulcer dyspepsia, but neither do they supply any evidence for a causal role.
Comment

*H. pylori* infection is common amongst patients with non-ulcer dyspepsia, however most of the data published to date has not been correlated with controls matched for age and ethnic group, making it very difficult to say whether or not there is a higher prevalence of *H. pylori* infection in patients with non-ulcer dyspepsia than in the general population. Figures from the ‘West’ suggest that there is a moderately higher prevalence, but there is no evidence for this in the ‘Developing World’.
Introduction

In the assessment of whether or not \textit{H. pylori} causes non-ulcer dyspepsia the gold standard must be the resolution of symptoms on eradication of the organism. It is symptoms which the patient complains of and not gastritis or \textit{H. pylori} infection. The resolution of gastritis is of little concern to the patient and at present of unknown significance to the clinician.

Trials of \textit{H. pylori} eradication in Non-ulcer Dyspepsia


None of these studies is adequate to demonstrate whether eradication of \textit{H. pylori} leads to an improvement in the symptoms of non-ulcer dyspepsia. While none are conclusive they do give some positive encouragement.
Conclusion

The question remains unanswered. \textit{H. pylori} is more prevalent amongst patients with non-ulcer dyspepsia, although not by much. The variations of prevalence in the normal population with age and ethnic group make the data available in dyspeptics difficult to interpret.

Treatment studies have been disappointing, in that they have not given a clear answer to whether or not \textit{H. pylori} causes symptoms, however most trials have shown greater improvement in symptoms on anti-\textit{H. pylori} treatment over and above placebo. It is reasonable to suggest that \textit{H. pylori} plays a role in the aetiology of non-ulcer dyspepsia, although the case is not yet proven.

Treatment of \textit{H. pylori}

\textit{H. pylori} is sensitive to a large number of anti-microbial agents in vitro (McNulty & Dent, 1988), but eradication of the organism in vivo has proved difficult. Initial attempts at treatment using, either a single antibiotic or, a bismuth compound attained clearance rates of 30-60\% (Rauws & Tytgat, 1989), however clearance was assessed at the end of treatment and it soon became apparent that many patients rapidly became re-infected after stopping treatment. Langenberg, et al (1986) demonstrated, using restriction endonuclease analysis, that this re-infection was in fact recrudescence of a previously suppressed but not eradicated organism. Rauws & Tytgat (1989) make the important distinction between clearance of the organism, as measured at the end of treatment and eradication, measured at least one month after discontinuing treatment, after which the organism is unlikely to recrudesce (Rauws et al, 1988).

Bismuth alone achieved clearance in 44 - 78\% of patients (Lambert et al, 1987, McNulty et al, 1986), but true eradication in a maximum of 33\%. These compounds whose antibacterial action against \textit{H. pylori} was first noted by

The best rates of *H. pylori* eradication with antibiotic monotherapy have been achieved with furazolidone (44%) (Gilman, 1987), amoxycillin (23%) (Rauws et al, 1988) and nitrofurantoin (22%) (Gilman, 1987).

These rather unspectacular results, similar to those obtained with bismuth led to the combination of the two compounds and subsequently to triple therapy, with two antibiotics and bismuth. Eradication rates of 33-75% (Bayerdorffer, et al, 1987, Goodwin, et al, 1987) have been achieved with double therapy and 81-94% (Rauws & Tytgat, 1989, Borody, et al, 1989) with triple therapy. While triple therapy does give good eradication rates there is a high level of side effects. Rauws & Tytgat (1989) found significant side effects in almost half of a group of 48 patients with non-ulcer dyspepsia treated with bismuth, amoxycillin and metronidazole.

**Comment**

Monotherapy with either bismuth or antibiotics gives poor eradication rates and high levels of bacterial resistance. Good eradication rates are possible with triple therapy, but only at the expense of considerable side-effects.
HELCOBACTER PYLORI: CONCLUSION

_H. pylori_, re-discovered and cultured by Marshall and Warren in 1983, is one of the commonest bacterial infections in man. In the normal population its prevalence increases with age and varies with ethnic group. _H. pylori_ causes type B gastritis and is the source of gastric urease. Its role in the aetiology of non-ulcer dyspepsia remains unclear. Eradication of the organism results in resolution of gastritis, but as yet the ideal treatment agent(s) does not exist.
THE TREATMENT OF NON-ULCER DYSPEPSIA

Introduction

As might be expected in a disease for which the cause is unknown, the treatment is uncertain and without a firm scientific basis. Several reviews on non-ulcer dyspepsia have commented on therapeutic options. Lagarde & Spiro (1984) divided treatment into three groups i) treatment directed at suppression or neutralization of acid, ii) treatment directed at enhancing gastrointestinal motility iii) psychological and emotional support therapy. Thompson (1984) does a good job at ‘debunking’ the issue, pointing out that there is no good evidence for an effect, over and above a placebo effect, of any of the agents commonly used for treating non-ulcer dyspepsia. However, apart from ‘reassurance’ he gives little advice on how these patients should be treated.

An anonymous editorial in the Lancet (1986) gives more definite advice, suggesting that patients should be treated with antacids on first presentation (because they are cheap!). Those patients with severe or persistent symptoms should then undergo endoscopy, for those with non-ulcer dyspepsia the therapeutic guidelines then become more obscure, with suggestions of a change of lifestyle, dietary changes, and antacids, or antispasmodics.

Acid Neutralisation

Antacids: Introduction: Non-ulcer dyspepsia is the most common reason for using antacids, Langman (1978) reported that one quarter of the population use antacids regularly each week. Mead et al (1977) in a study of 100 dyspeptic patients below the age of 50, found that 91% reported the regular use of antacids, a practise continued despite a ‘negative work up’. Such figures must mean that either the patient, the doctor or both believe that antacids have a beneficial effect in non-ulcer dyspepsia.

**Acid Supression: H2 Blockade:** The results of the double blind, placebo controlled trials using H2 blockade for acid supression have been disappointing, with the majority of studies not showing a significant difference (see Table 7).

**Motility Enhancement:** The available double blind trials have been reviewed in the section on dysmotility above, generally these drugs have shown a better response over placebo, but in a select group of patients, particularly those in whom nausea and vomiting, abdominal distension and early satiety are prominent symptoms.

**Cytoprotection:** Sucralfate is a cytoprotective drug that forms an adherent complex with proteins of the damaged and normal gastroduodenal mucosa and thus acts as an effective barrier against the deleterious actions of acid, pepsin, and bile salts (Nagashima, 1981). Kairaluoma, et al (1987) used sucralfate in a double blind placebo controlled trial of 151 patients with non-ulcer dyspepsia and found a significantly better response with sucralfate compared to placebo (77% vs 56%).

**H.pylori Eradication:** The trials of *H.pylori* eradication in non-ulcer dyspepsia have been reviewed above, they are inconclusive, but do generally show a better therapeutic response than placebo.

**Comment**

There is no single agent with good, reliable, scientifically proven efficacy in the treatment of non-ulcer dyspepsia.
THE DIFFERENTIAL DIAGNOSIS OF NON-ULCER DYSPEPSIA IN AFRICA

Introduction

As discussed previously (see ‘Definition of non-ulcer dyspepsia’) the upper gastrointestinal tract has a limited number of symptomatic responses, consequently many different pathologies present with dyspepsia. In most patients with a particular cause for their dyspepsia this can be elucidated on the basis of history and examination, supplemented by a small number of investigations. The following section briefly discusses the common differential diagnoses for dyspepsia in Africa.

PARASITES

Parasitic infection is common throughout Africa and is said to be an important cause of dyspepsia (Archampong, 1984). Hookworm is most commonly implicated in the cause of epigastric pain, a uniform finding in infection, leading to possible confusion with peptic ulceration (Muller, 1979).

Taenia, Ascaris lumbricoides, Giardia duodenalis and Entamoeba histolytica have all been reported as causing abdominal pain, but the majority of people infected are asymptomatic (Soulsby, 1975, Meyer & Radulescu, 1978, Elsdon-Drew, 1968).

Comment

Both dyspepsia and parasitic infestation are common in Africa. It is easy to assume that these are causally related, which is probably not the case in many patients.
GALLSTONES

Gallstones in Africa

Gall bladder disease can cause dyspepsia, however gallstones are much less common in Africa than in the 'West'. In East Africa, Vint (1937) found gallstones in only one of 1,000 consecutive autopsies, while Owor in 1964 found gallstones in 59 (0.87%) of 6,773 autopsies in Kampala, Uganda.

Clinicians working in Africa have confirmed this paucity of gallstones; Shaper & Patel (1964) found only 22 cases of proved biliary tract disease among 61,000 admissions in Uganda. A retrospective questionnaire of 25 doctors with extensive clinical experience in Africa could reveal no single case (Burkitt & Tunstall, 1975).

Gallstones may be coming more common in some areas. Parnis in 1964 reported 25 patients operated on for gallstones during a five year period at University Hospital, Ibadan. Adedeji in 1986 reported on 69 cases of cholecystitis over a 5 year period in Lagos, suggesting that increasing Westernisation was leading to an increase. Gallstones are more common in patients with sickle cell disease (up to 25%) (Durosinmi, et al, 1989), although less common than in Americans with sickle cell disease (Adekelie, 1985).

TROPICAL PANCREATITIS

Abdominal pain is one of the main symptoms of patients with chronic pancreatitis (Sarles, 1972), this pain is often epigastric so that chronic pancreatitis is one of the differential diagnoses for non-ulcer dyspepsia, however patients with chronic pancreatitis usually have other features of the disease.

Africa

In Africa the syndrome of tropical pancreatitis has been described. This is characterised by chronic, calcific pancreatitis developing early in life,
unassociated with biliary disease or alcoholism, which is manifest as diabetes mellitus (Banwell, et al, 1967). Shaper (1959) described 11 patients with pancreatic calcification in Uganda, East Africa and found both malnutrition and diabetes to be common. Kinnear (1963) found a similar syndrome among diabetics in Nigeria. More recently two studies from South Africa have shown an increasing incidence (Akoojee, 1978, Segal, et al, 1988) of pancreatitis.

**Comment**

Epigastric and abdominal pain occur frequently in chronic tropical pancreatitis, however almost invariably this is associated with other features of pancreatic dysfunction, commonly diabetes and/or steatorrhea.

**HIATUS HERNIA & GASTRO-ÖESOPHAGEAL REFLUX**

**Symptoms**

The ‘Management of Dyspepsia Working Party’, under the chairmanship of Dr Duncan Colin-Jones (Colin-Jones, 1988) divided dyspepsia into five categories on the basis of symptoms one of which was ‘gastro-oesophageal reflux-like dyspepsia’, which they state is not usually difficult to diagnose on the basis of the history.

**Prevalence**

Heartburn and hiatus hernia are common in the West (Nebel et al, 1976) but uncommon in Africa. Bassey, et al (1977) studied 1030 patients prospectively and looked specifically for evidence of hiatus hernia and gastro-oesophageal reflux at barium meal examination, he found a very low incidence of hiatus hernia (0.39%) and of gastro-oesophageal reflux (2.2%), findings confirmed by Segal et al (1980) in South African Blacks who found hiatus hernia in 46 of 1392 (3.3%).
Dyspepsia is difficult to define, but has plagued man since the beginning of history, and has been recognized in Africa, since the keeping of records. With the arrival of reliable diagnostic methods at the beginning of this century it became apparent that many people with dyspepsia did not have an ulcer and so a new disease, non-ulcer dyspepsia, was born.

Non-ulcer dyspepsia is common in the 'West' and in Africa, with up to 30% of the population complaining of symptoms, which are a source of considerable morbidity and expense to the health care system.

The cause of non-ulcer dyspepsia is not known, indeed it is probably a collection of several different pathologies all presenting to the physician with a similar symptom complex. It seems likely that in the small proportion with duodenitis hyperacidity is involved in the aetiology, while there is another group in which dysmotility may play a role. More recently Helicobacter pylori has been suggested as the cause.

*H. pylori* was discovered in 1983 and has now been shown to be the cause of type B, antral gastritis. There is also an association with non-ulcer dyspepsia and trials of anti-*H. pylori* treatment, in patients with non-ulcer dyspepsia, although not conclusive, have shown improvement of symptoms in some suggesting that *H. pylori* may play a role in the aetiology of non-ulcer dyspepsia.

There is little information available on *H. pylori* in Africa, but the data available suggests that both antral gastritis and *H. pylori* infection are more common than in the 'West'. A particularly high level of *H. pylori* infection has been reported in patients with dyspepsia and it is reasonable to suggest that
*H. pylori* might be the cause of non-ulcer dyspepsia in Africa.

The ideal treatment for *H. pylori* infection does not exist; monotherapy gives very poor rates of eradication, while triple therapy has a very high incidence of side effects, double therapy is a reasonable compromise, with a combination of a bismuth compound and antibiotic being the most effective.

In any consideration of non-ulcer dyspepsia in Africa the common differential diagnoses must be considered.
CHAPTER 3

HYPOTHESIS & STUDY OUTLINE
As a result of the pilot study and literature review the following hypothesis has been formed:

**HYPOTHESIS**

It is hypothesised that Helicobacter pylori is the cause of non-ulcer dyspepsia in Northern Nigeria.

**STUDY OUTLINE**

The monofactorial approach to disease causation probably originated with Pasteur who first linked specific diseases with specific bacteria (Correa, 1991). The proof of causality was then defined by Koch's postulates (Talbot, 1970). Briefly these state: 1 That the organism should be found in the body of animals with the disease in question. 2 That the organism should be obtained from the diseased animal and grown outside the body. 3 The organism should be able to infect normal animal and 4 cause the disease in question.

The first study detailed in chapter 4 attempts to investigate Koch's first and second postulates. However the majority of subjects in northern Nigeria acquire \textit{H. pylori} infection at a young age (see chapter 5, pg.110) and it is therefore very difficult to prove Koch's third and fourth postulates for non-ulcer dyspepsia in northern Nigeria. Indeed with a disease such as non-ulcer dyspepsia in which several factors may act together to cause symptoms, the criteria of Bradford-Hill (1965) for disease causation are probably more appropriate and
Indeed Koch’s first and second postulates merely demonstrate association and not cause, it is vital to measure the prevalence of \textit{H. pylori} infection in the general population and in controls without dyspepsia. This is the aim of studies two and three; an epidemiological survey of the prevalence of antibodies of \textit{H. pylori} in the rural population and a volunteer study of the prevalence of \textit{H. pylori} and gastritis in a control population without dyspepsia. These studies enable assessment of the first and second criteria of Bradford-Hill (see pg.144).

Finally, if \textit{H. pylori} is the cause of non-ulcer dyspepsia then its elimination will result in the resolution of symptoms, which will not resolve in those in whom \textit{H. pylori} remains, Bradford-Hill criterion number 7 (see pg.144). This is the aim of the fourth study, a therapeutic trial comparing bismuth and amoxycillin, (a combination which is bactericidal to \textit{H. pylori}), with Gelusil, (an aluminium hydroxide and magnesium trisilicate combination antacid tablet), which does not cause elimination of \textit{H. pylori} (Berstad, et al, 1990).
CHAPTER 4

HELIcobacter pylori infection & gastritis in patients with non-ulcer dyspepsia
INTRODUCTION

For *H. pylori* to have an aetiological role in non-ulcer dyspepsia, the bacteria must be found in those suffering from non-ulcer dyspepsia. This study analyses the patient population presenting with non-ulcer dyspepsia and records the incidence of gastritis and *H. pylori* infection within this group.

MATERIALS & METHODS

**Definition of non-ulcer dyspepsia**

Non-ulcer dyspepsia was defined according to the definition of the management of dyspepsia working party (Colin-Jones, 1988), with the exception that patients in whom nausea and vomiting, prominent 'gaseous symptoms', or symptoms of gastro-oesophageal reflux were pre-eminent, were excluded. This is comparable to the categories of ulcer-like dyspepsia, as defined by Colin-Jones (1988) and essential dyspepsia as defined by Talley and Phillips (1988). In practise patients were recruited for the study if they fulfilled the following strict entry and exclusion criteria.

**Entry Criteria:** Patients who had chronic epigastric pain of at least three months duration plus two of the following: exacerbation or relief by meals, exacerbation by hunger, night waking, heartburn, relief of pain by antacids or milk, epigastric tenderness.

**Exclusion Criteria:** Patients who had taken antibiotics, bismuth containing compounds, or anti-ulcer drugs other than simple antacids in the previous month. Patients who were seriously ill, pregnant, or had undergone previous upper gastrointestinal surgery. Patients who had experienced less than four episodes of pain in the preceding two weeks. Those with other pathology which may have accounted for the dyspepsia eg. irritable bowel syndrome (diagnosed according to the criteria of Manning, et al, (1978)), gall bladder disease, or tropical pancreatitis. Those with symptoms suggestive of gall bladder disease had an oral cholecystogram.
**Patient Recruitment**

Patients were recruited from Maiduguri and Borno State. All the patients presenting to the University of Maiduguri Teaching Hospital with dyspepsia were referred to me for further assessment and possible endoscopy. The sample is reasonably representative of the population of Maiduguri, but inevitably those who are better educated and richer than the average, tend to make better use of the medical facilities and may be over represented.

**Baseline Assessment and Gastroscopy**

Once it was decided that patients were eligible for entry into the study, a detailed proforma was completed (see Appendix 4, pg 155) for each patient and their symptoms were scored (see pilot study for details). Patients then underwent day case gastroscopy. The patients were sedated with intravenous diazepam, and the pharynx was anaesthetised with 5% topical xylocaine spray. The endoscopy was done with an Olympus GIF-Q10, fully immersible gastroscope.

Each gastroscopy was carried out in a standard manner with two mucosal biopsies taken from the antrum within two centimetres of the pylorus, one for culture and one for histology. A further biopsy was then taken from the body of the stomach close to the angulus, this was also sent for histology. In addition any other abnormal features were biopsied and sent for histology. Patients with non-ulcer dyspepsia were randomised to one of the two trial treatment arms (see chapter 7). Patients had a fresh stool sample microscoped for parasites by the Microbiology Department.

**Cleaning and Care of Gastroscope**

One of a team of four specially trained nurses was responsible for assisting at the gastroscopy lists and for care of the gastroscope.
Before Gastroscopy: The biopsy and suction channels were irrigated with 2% activated glutaraldehyde (Cidex, Johnson & Johnson) using the all channel irrigator and then the whole scope was immersed in glutaraldehyde for 20 minutes. Immediately before use, the scope, and all its channels, were washed in water to remove all the disinfectant. The suction valves, air, water and biopsy valves were fitted ready for use. The same procedure was repeated, between cases except that the scope was soaked in activated glutaraldehyde for ten minutes only. The cleaning procedure was repeated again at the end of the list. The scope was soaked in glutaraldehyde for 20 minutes, before being rinsed, dried, and hung up. Maintenance and repair were carried out by Keymed UK.

Statistical Analysis
Confidence limits were calculated for the symptom scores and the Chi squared test to compared those with and without H. pylori infection.

Histology
Specimens were fixed in 10% formalin and sent by courier and post to University College and Middlesex School of Medicine, Department of Histopathology, in London. Here they were processed, embedded in paraffin wax, sectioned and stained using haematoxylin and eosin. The sections were then examined for the presence of H. pylori and gastritis, by Dr Sebastian Lucas.

Microbiology
One antral biopsy was sent to the microbiology laboratory for culture, which was done by Miss H. Umar and Mr Habila, lecturers in the Department of Microbiology, at the University of Maiduguri Teaching Hospital (see appendix 2 for details). When possible the specimens were transferred to the laboratory within three hours, however a microbiologist was not always present, and so not all patients had cultures done and some specimens were delayed for more than three hours.
Diagnosis of Gastritis and H. pylori Infection

Gastritis and H. pylori infection were both diagnosed on the basis of histological examination of mucosal biopsies.

**Gastritis:** Several studies have demonstrated poor correlation between macroscopic findings of gastritis and the histological diagnosis of gastritis (Sauerbruch, et al, 1987, Myren & Serck-Hanssen, 1974). This fact was recognised, and while macroscopic findings were recorded the diagnosis of gastritis was based on histological examination, according to the criteria of Whitehead, et al (1972). Normal gastric mucosa is pictured in figures 16 & 17, and typical gastritis in figures 18 & 19 (gastric mucosal biopsies from the patients studied).

**Fig.16.** Normal gastric antrum (haematoxylin & eosin)
Fig. 17. Normal gastric fundus (haematoxylin & eosin).

Fig. 18. Active antral gastritis (haematoxylin & eosin).
**H. pylori Infection:** Mucosal biopsies were stained with haematoxylin & eosin and *H. pylori* infection diagnosed by virtue of their characteristic morphology and position (see figures 20 & 21). This method had been previously validated by Wyatt, et al (1988b), who concluded that two mucosal biopsies are sufficient for reliable diagnosis. Culture of the biopsies confirmed the presence of *H. pylori* infection, but was not sufficiently reliable for routine diagnosis.
Fig. 20. *H. pylori* in antral biopsy (haematoxylin & eosin).

Fig. 21. *H. pylori* in antral biopsy (haematoxylin & eosin).
RESULTS

153 patients fulfilled the entry criteria and underwent upper gastrointestinal endoscopy, 10 duodenal ulcers, 2 patients with the stigmata of ulcer (1 pyloric stenosis, 1 deformed bulb) and 2 gastric ulcers (1 pre-pyloric) were seen and in 1 patient the biopsies taken were inadequate for assessment, leaving 138 patients with non-ulcer dyspepsia (90%) who were assessed.

Table 18: Characterisation of Patients with Non-Ulcer Dyspepsia

<table>
<thead>
<tr>
<th>Sex</th>
<th>Male</th>
<th>61</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>77</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>138</td>
</tr>
<tr>
<td>Age:</td>
<td>Mean</td>
<td>29 years</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>13-67</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>27</td>
</tr>
<tr>
<td>Tribe:</td>
<td>Northern</td>
<td>126 (91%)</td>
</tr>
<tr>
<td></td>
<td>Southern</td>
<td>12 (9%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td>6 (4.3%)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td>2 (1.4%)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td>34 (24%)</td>
</tr>
<tr>
<td>Education</td>
<td>Nil</td>
<td>32 (23%)</td>
</tr>
<tr>
<td></td>
<td>Primary</td>
<td>18 (13%)</td>
</tr>
<tr>
<td></td>
<td>Secondary</td>
<td>41 (29%)</td>
</tr>
<tr>
<td></td>
<td>Polytechnic</td>
<td>11 (8%)</td>
</tr>
<tr>
<td></td>
<td>University</td>
<td>34 (24%)</td>
</tr>
</tbody>
</table>

Dyspepsia

The length of episodes of pain varied from 5 minutes to all day (720 minutes), with a mean of 131 minutes (median 60 minutes). In 78 (56%) patients the pain was severe enough to stop the patients daily activity. The commonest exacerbating factors were hunger 118/138 (85.5%) and pepper 115/138 (83%).
Culture

Culture was attempted in 61 patients; 31 were positive, and 25 negative, 3 were too heavily contaminated for assessment and 2 biopsies dried out. Of the 26 negative cultures \textit{H.pylori} were seen in 23 on histology. All patients from whom \textit{H.pylori} was cultured also had \textit{H.pylori} diagnosed histologically.

Table 19: Symptom Score according to \textit{H.pylori} Status

<table>
<thead>
<tr>
<th>No.pts.</th>
<th>Symptom Score</th>
<th>95% Conf. Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
</tr>
<tr>
<td>Total:</td>
<td>138</td>
<td>30</td>
</tr>
<tr>
<td>Patients \textit{H.pylori} +ve:</td>
<td>122</td>
<td>30</td>
</tr>
<tr>
<td>Patients \textit{H.pylori} -ve:</td>
<td>18</td>
<td>33</td>
</tr>
</tbody>
</table>

Table 20: Macroscopic Findings on Endoscopy in Patients with Non-ulcer Dyspepsia:

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>84</td>
</tr>
<tr>
<td>Polyp</td>
<td>5</td>
</tr>
<tr>
<td>Gastritis: Antral</td>
<td>23</td>
</tr>
<tr>
<td>Biliary reflux</td>
<td>3</td>
</tr>
<tr>
<td>Body</td>
<td>6</td>
</tr>
<tr>
<td>Erosions</td>
<td>3</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>22</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>1</td>
</tr>
</tbody>
</table>

69 lesions in 54 patients with macroscopic pathology (39%).

Table 21: Histological Findings (see figure 22)

- Gastritis: 126/138 (91%)
- \textit{H.pylori} infection: 120/138 (87%)
- \textit{H.pylori} infection was present in: 120/126 patients with gastritis (95%)

There was a strong correlation between the presence of \textit{H.pylori}
infection and histological gastritis. In the 12 patients who had a histologically normal gastric mucosal biopsy, none were infected by \textit{H. pylori}. In those with gastritis \textit{H. pylori} infection was present in 120/126 (95%), the difference is statistically highly significant (p<0.001). \textit{H. pylori} infection was found in 53/56 (95%) patients who had a positive finding on endoscopy.

Fig. 22. Histological findings in patients with non-ulcer dyspepsia.

Correlation between Endoscopic and Histological Findings

All patients who had macroscopic gastritis had this confirmed histologically, although in 97 patients, mucosal biopsies demonstrated histological gastritis despite a normal looking mucosa at endoscopy.

	extbf{Intestinal Parasites}

Parasites were found in 24 of 84 (28.6%) patients tested.

\begin{itemize}
  \item \textit{Entamoeba histolytica} - 16
  \item \textit{Hookworm} - 4
  \item \textit{Giardia duodenalis} - 3
  \item \textit{Ascaris lumbricoides} - 1
  \item \textit{Schistosoma mansoni} - 1
\end{itemize}
DISCUSSION

The majority of patients presenting with dyspepsia in northern Nigeria, have non-ulcer dyspepsia, and amongst these patients 91% have gastritis and 87% *H. pylori* infection. Over 95% (120/126) of patients with gastritis are infected by *H. pylori*.

The culture results were helpful in proving conclusively that the spiral organisms seen histologically were *H. pylori*, but the technique was not reliable enough for diagnosis. All the patients from whom *H. pylori* was cultured had *H. pylori* detectable histologically.

*H. pylori* is a difficult organism to culture and a marked learning curve was apparent. Culture was successful in only 7 of the first 20 patients (35%) in whom *H. pylori* was diagnosed histologically, but 15 of 20 specimens (75%) cultured at the end of the study. This was partly due to the introduction of selective Skirrows medium. There were unfortunately often delays in the processing of these specimens which probably accounted for the failure of culture in the remaining 25%.

The number of patients with non-ulcer dyspepsia is much higher than has been reported in similar series in the ‘West’. Since 1975 (the approximate time when flexible endoscopy came into widespread use) the mean percentage of patients with non-ulcer dyspepsia in published series has been 36%, (Thompson, 1984) just over a third of the incidence in this study. However this high proportion of non-ulcer dyspepsia is a feature of the reports from Africa, where the mean percentage of patients with non-ulcer dyspepsia is 78%, over double that found in the 'West' (see figure 23). This finding may be accounted for by the young age of the populations concerned, the incidence of upper gastrointestinal pathology rises with age and one would expect to find comparitively little pathology in patients of 29 years, the mean age of patients in this study.
The prevalence of *H. pylori* infection at 120/138 (87%) is higher than in any series reported from 'Western' populations, where the highest prevalence is 74% from Italy (Fiocca, 1987), with a range of 33 - 74% in seven studies (see Table 15). However the prevalence rates are similar to those found in other studies from Africa, where prevalence rates of 68-100% have been reported (see figure 24).

**Fig.24.** Prevalence of *H. pylori* infection in patients with dyspepsia in Africa.
The prevalence of gastritis is also much higher than is found in 'Western' populations. The strong association between *H. pylori* infection and gastritis in this study confirms the findings in the 'West' that *H. pylori* causes gastritis. There is very poor correlation between the histological and endoscopic findings of gastritis. In the majority of patients the mucosa looked normal, despite the presence of histological gastritis, thus confirming the findings of Sauerbruch, et al (1987) and Myren & Serck-Hanssen (1974)

**CONCLUSION**

This study reveals a strong association between non-ulcer dyspepsia and *H. pylori* gastritis and suggests that there may be an aetiological link between *H. pylori* and non-ulcer dyspepsia.
CHAPTER 5

THE PREVALENCE OF ANTIBODIES TO HELICOBACTER PYLORI IN THE
COMMUNITY:

A RANDOM SEROLOGICAL SURVEY
INTRODUCTION

The prevalence of *H. pylori* infection varies with age and ethnic group and although the preceding study into the prevalence of *H. pylori* infection and gastritis in patients with non-ulcer dyspepsia showed very high levels of infection and gastritis it is important that this is put into the context of the level of infection in northern Nigeria in the general population. This study is designed to determine the prevalence of IgG antibodies to *H. pylori* in a randomly chosen rural population of different ages.

MATERIALS & METHODS

**Study Population**

This study took place in five villages, within Konduga local government, close to the state capital, Maiduguri (see figure 25). These are small rural villages with populations of three to five hundred. The people live in mud houses, with thatched roofs, water is collected from stand pipes supplied from an underground source by a bore hole, sewage is disposed of using pit latrines. The majority of the population are subsistence farmers, although a small proportion, those from the Fulani tribe, keep cows and sheep, the majority of the population are from the Kanuri tribe. Few of the population can read or write (approx. 1%), a similar proportion had completed primary school and an even smaller proportion had received secondary education.

**Sampling**

Each village is divided into wards and the houses in each ward had been previously numbered as part of the primary health care programme. Households were sampled from each of the wards in the village, using a table of random numbers.

Within each household all occupants over the age of 5 years were interviewed and requested to give a 5ml blood sample. Not all subjects were
prepared to give blood, in which case the interviewers moved on to the next randomly chosen household.
Data Collection

Interviewing and blood sampling was done by medical students with the help of village health workers as interpreters, when necessary. A questionnaire was completed for each subject, the first part detailed basic demographic details, the second part was completed if subjects had dyspepsia (as defined in Chapter 4).

Statistical Analysis

Confidence limits were calculated for the prevalence of antibodies to \textit{H.pylori} in each age group.

Serum Testing

Serum was tested at the Public Health Laboratory, in Manchester, UK by Dr. J. Eldridge, under the guidance of Dr. D.M. Jones. The serum was dried on filter paper and sent by courier and post, this was eluted on arrival in the laboratory. Specimen samples collected and dried on filter paper have been used for the detection of markers of hepatitis B (Zhuang, et al, 1982), for the detection of antibodies to the human immunodeficiency virus (Parzadegan, et al, 1987) and more recently \textit{H.pylori} (Huang, et al, 1991). This is a well tried method which was further tested in the present study; serum samples were dried on filter paper and left for up to one month at room temperature, to simulate conditions during transport, this was done without significant loss of antibody activity (Jones, personal communication). The serum was tested using a standard enzyme linked immunosorbant assay (ELISA) technique (Voller & de Savigny, 1981) to detect IgG antibodies to whole cell \textit{H.pylori} antigens. This was a technique previously validated in the UK. (Jones, et al, 1986), for details of technique see appendix 3.

Some of the surface antigens for \textit{H.pylori}, in particular the flagella proteins, have epitopes in common with Campylobacter jejuni (Newell & Stacey, 1989) and therefore all sera were absorbed with C.jejuni before testing for \textit{H.pylori} antibodies.

In any ELISA the optical density cut off level for validated negatives must be determined. This is particularly true of the present study where, due to the handling of the serum, and pre-absorption with C. jejuni, the resulting optical density levels may not be exactly the same as might be obtained with serum from the UK.
Determination of the Optical Density Cut Off Level for Validated Negatives

The ELISA optical density was measured on the serum of thirty patients known to be infected by *H. pylori* from the results of culture and histological examination of endoscopic biopsies. These optical densities were plotted on a scattergram (see figure 26), and were all above 0.500, with a mean of 0.900. In a search for uninfected subjects, two further groups were studied; Nigerian infants aged six months to two years (*n*=21), and British expatriates living in Nigeria (*n*=11). The scattergram of these subjects (see Figure 26) shows the optical densities clearly divided into two groups, below 0.4 (uninfected) and above 0.6 (infected), with a small number of subjects in between. On the basis of this the negative optical density reading for this assay was established at <0.5.

Fig.26. Scattergram of ELISA optical densities.
The validity of this level was confirmed by comparing the prevalence of \textit{H}.\textit{pylori} antibody found in the serological survey, with the prevalence of antibody in an age matched group of asymptomatic volunteers (n=40), who had their infection confirmed by histological examination. The mean age of this asymptomatic group was 23 years, of whom 85\% were infected by \textit{H}.\textit{pylori}, compared with 79\% in the community (age 20-29).

**RESULTS**

Serum was collected from 268 subjects, 151 male and 117 female, over the age of 5 years, the mean age of the sample was 35 years (range 5 - 80), of whom 228 (85\%) had antibodies to \textit{H}.\textit{pylori}. All the subjects were from northern Nigeria, mostly from the Kanuri ethnic group (81\%).

\textbf{Table 22}: Patients positive and negative for antibodies to \textit{H}.\textit{pylori} according to age (see figure 27).

<table>
<thead>
<tr>
<th>Age</th>
<th>5-9</th>
<th>10-19</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>60+</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers</td>
<td>17</td>
<td>39</td>
<td>75</td>
<td>68</td>
<td>38</td>
<td>16</td>
<td>15</td>
<td>268</td>
</tr>
<tr>
<td>Number +ve</td>
<td>14</td>
<td>36</td>
<td>59</td>
<td>53</td>
<td>36</td>
<td>16</td>
<td>14</td>
<td>228</td>
</tr>
<tr>
<td>%</td>
<td>82%</td>
<td>92%</td>
<td>79%</td>
<td>78%</td>
<td>95%</td>
<td>100%</td>
<td>93%</td>
<td>85%</td>
</tr>
<tr>
<td>95% Conf.+/Limits</td>
<td>18.3%</td>
<td>8.5%</td>
<td>9.2%</td>
<td>9.8%</td>
<td>6.9%</td>
<td>4.9%</td>
<td>12.9%</td>
<td>4.3%</td>
</tr>
</tbody>
</table>

Of the 268 randomly chosen subjects 58 had experienced dyspepsia, the mean age of this group was also 35 years. Forty seven (81\%) had antibodies to \textit{H}.\textit{pylori}, and 11 (19\%) were negative (see figure 28).
Fig. 27. Prevalence of IgG antibodies to *H. pylori*, according to age group.

Fig. 28. Antibodies to *H. pylori* in subjects with & without dyspepsia.
DISCUSSION

The level of antibodies to *H. pylori* in this community is the highest that has been reported. These antibodies are likely to represent active infection with *H. pylori* as IgG antibody levels return to normal over approximately eighteen months, when infection has been eradicated (Veenendall, et al, 1990). In comparison with studies from the 'West' the most striking feature is the large number of people who are infected under 10 years. A level of infection of 92% in teenagers is exceptionally high when compared with 4% from the UK. (Jones, et al, 1986), 18% from France (Megraud, et al, 1989) and 11% from Australia (Dwyer, 1989) (see figure 29).

**Fig.29.** Comparison of prevalence of *H. pylori* infection in the developing world & Western population.
Eighty five percent (95% confidence limits: 80.7 - 89.3%) of the population over the age of five, in Northern Nigeria, have IgG antibodies to \textit{H. pylori}. Such high levels of infection, if found throughout Africa, make this one of the commonest bacterial infections on the continent. Why \textit{H. pylori} infection is more common in Africa than the 'West' is unknown. It is suggested in the literature that \textit{H. pylori} infection is acquired by person to person contact (see literature review) and that it is more common in populations that are less developed and have lower standards of hygiene, as found in rural Nigeria.

The ideal antigen for use in an ELISA needs to have high sensitivity and specificity, as well as be practical to use and to prepare (Newell & Stacey, 1989). Initially whole cell antigens were used, as in this study, however these antigens tend to have high backgrounds, and cross react with other organisms, particularly \textit{C. jejuni}. Recently more specific antigens have been used, these can give increased specificity, without a loss of sensitivity. Newell & Stacey (1989b) describe the use of a acid extract antigen, while Hirschl et al (1990) obtained a sensitivity of 97% and specificity of 98% by combining an ultra-centrifuged sonicate and acid glycine extract. In this study whole cell antigens were used, but the sera were preabsorbed with \textit{C. jejuni} to remove the major source of cross reactivity, although it is possible that some cross reactivity with other bacteria remained.

The cut off level for validated negatives is usually determined with reference to the optical densities found in subjects found to be negative by other diagnostic methods. In northern Nigeria this is a particular problem due to the very high prevalence of \textit{H. pylori} infection, hence the determination of the optical density cut off level for validated negatives as detailed in the methods (pg.114-115).

The optical density cut off level for validated negatives, set at 0.5,
is believed to give the best specificity and sensitivity for this test as used. The prevalence of *H. pylori* infection, determined by histology and culture in age matched controls is very similar (see chapter 6, pg.120), to that determined by serology and provides strong corroboration evidence that the negative cut off level has been correctly set. However the problems and limitations of the methodology must be born in mind when interpreting the results.

With such high levels of infection, one must doubt the pathological significance of the organism. Interestingly, there is no significant difference between the levels of infection in subjects with and without dyspepsia, in fact the level of infection is marginally higher in subjects who have not had dyspepsia.

It may be that *H. pylori* does cause antral gastritis even in those who are asymptomatic, a question addressed in the next chapter, but whether or not this has any further clinical significance remains open to debate.

Certainly *H. pylori* acting alone cannot be the cause of non-ulcer dyspepsia, as most of the population are infected with *H. pylori* and are asymptomatic. However a role for *H. pylori*, in combination with other factors, cannot be ruled out. This is addressed further in chapter 7.

**CONCLUSION**

These results are in stark contrast to those found in the ‘West’ and suggest that the association between *H. pylori* gastritis and non-ulcer dyspepsia in the preceding chapter may be coincidental. The difference between the prevalence of *H. pylori* infection in patients with non-ulcer dyspepsia (87%) and the prevalence in the general population (85%) is statistically insignificant.

Patients with non-ulcer dyspepsia and the villagers tested in this study are from the same ethnic group, but are not well matched for other factors, furthermore it is not possible to assess the prevalence of asymptomatic ulcer or gastritis in a serological survey. These problems are addressed in the next chapter.
CHAPTER 6

CASE CONTROL STUDY:
HELIcobacter pylori AND GASTRITIS IN PATIENTS WITH
NON-ULCER DYSPEPSIA AND ASYMPTOMATIC VOLUNTEERS
INTRODUCTION

This study looks at the prevalence of *H. pylori* infection, gastritis and macroscopic pathology in a group of asymptomatic volunteers matched for age, sex, religion, ethnic group, and education, with a group of patients with non-ulcer dyspepsia.

METHODS

Asymptomatic, healthy volunteers were recruited, mainly from amongst hospital staff, medical students and acquaintances. Thirty naira (£1.50) was offered to those who participated. Great care was taken to exclude anyone who had had any upper gastrointestinal pain or symptoms in the preceding two years, or anyone who had a past medical history of peptic ulcer, had been investigated for dyspepsia or took antacids.

On entry into the trial each subject had a standard proforma completed, to document personal and demographic details. Subjects then underwent upper gastrointestinal endoscopy, at which two antral biopsies and one gastric body biopsy were taken from the stomach. Diagnosis of *H. pylori* infection and gastritis was based on histological examination as described in chapter 4.

On the completion of the study each asymptomatic volunteer was matched with a patient with non-ulcer dyspepsia, chosen from a group of 138 patients with non-ulcer dyspepsia. The matching was done without knowledge of the *H. pylori* status of either the asymptomatic controls or the patients with non-ulcer dyspepsia. An exact match was achieved for age, sex, ethnic group and religion and a close match achieved for the level of education (see table 23). This study was approved by the University of Maiduguri Research and Ethics Committee.
**Statistical Analysis**

The Chi squared test with Yates correction was used to compare the two groups.

**RESULTS**

There were forty patients in each group, 36 male and 4 female, 18 Muslims and 22 Christians, both groups had a mean age of 25 years, and in each group 36 were from northern tribes and 4 from southern tribes.

**Table 23: Baseline Data: Case Control Study**

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic Controls (40)</th>
<th>Cases (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>Female</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Age:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>Range</td>
<td>18-38</td>
<td>19-38</td>
</tr>
<tr>
<td>Median</td>
<td>24.5</td>
<td>24</td>
</tr>
<tr>
<td><strong>Religion:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muslim</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>Christian</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td><strong>Tribe:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>‘Northern’</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>‘Southern’</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td><strong>Education:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nil</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Primary</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Secondary</td>
<td>15</td>
<td>14</td>
</tr>
<tr>
<td>Polytechnic</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>University</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Table 24: Comparison of Cases and Asymptomatic Controls

<table>
<thead>
<tr>
<th>Environmental Factors</th>
<th>Asymptomatic Controls</th>
<th>Cases</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>6/40 (15%)</td>
<td>2/40 (5%)</td>
<td>1.335 p&lt;0.5 ns</td>
</tr>
<tr>
<td>Cola Nut</td>
<td>15/23 (65%)</td>
<td>13/40 (30%)</td>
<td>5.075 p&lt;0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>6/40 (15%)</td>
<td>2/40 (5%)</td>
<td>1.335 p&lt;0.5 ns</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>3/38 (8%)</td>
<td>5/40 (13%)</td>
<td>0.881 p&gt;0.5 ns</td>
</tr>
<tr>
<td>Parasites</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>3/16 (19%)</td>
<td>7/23 (30%)</td>
<td>0.329 p&lt;0.1 ns</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>2/16 (12.5%)</td>
<td>4/23 (17%)</td>
<td></td>
</tr>
<tr>
<td>Hookworm</td>
<td>1/16 (6%)</td>
<td>1/23 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2/23 (9%)</td>
<td></td>
</tr>
<tr>
<td>Macroscopic Pathology:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral gastritis</td>
<td>11/40 (28%)</td>
<td>18/40 (45%)</td>
<td>1.947 p&lt;0.5 ns</td>
</tr>
<tr>
<td>Biliary reflux</td>
<td>8/40 (20%)</td>
<td>9/40 (23%)</td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>2/40 (5%)</td>
<td>1/40 (2.5%)</td>
<td></td>
</tr>
<tr>
<td>Duodenitis</td>
<td>1/40 (2.5%)</td>
<td>5/40 (12.5%)</td>
<td></td>
</tr>
<tr>
<td>Body erosion</td>
<td>-</td>
<td>3/40 (7.5%)</td>
<td></td>
</tr>
<tr>
<td>Body gastritis</td>
<td>-</td>
<td>2/40 (5%)</td>
<td></td>
</tr>
<tr>
<td>Polyp</td>
<td>-</td>
<td>2/40 (5%)</td>
<td></td>
</tr>
</tbody>
</table>

Histological Findings (see Figures 30 & 31)

<table>
<thead>
<tr>
<th>Histological Gastritis</th>
<th>Asymptomatic Controls</th>
<th>Patients with Non-ulcer Dyspepsia</th>
</tr>
</thead>
<tbody>
<tr>
<td>H.pylori infection</td>
<td>35/40 (87.5%)</td>
<td>36/40 (90%)</td>
</tr>
</tbody>
</table>

ns: not significant

Fig.30. Gastritis in asymptomatic controls and patients with non-ulcer dyspepsia.
Fig. 31. *H. pylori* infection in asymptomatic controls and patients with non-ulcer dyspepsia.

![Diagram showing H. pylori infection rates]

Asymptomatic Controls (n = 40)  
 Patients with Non-ulcer Dyspepsia (n = 40)

**DISCUSSION**

There is no significant difference in the prevalence of *H. pylori* infection or gastritis between the two groups (see figures 30 & 31), suggesting that *H. pylori* acting alone does not cause non-ulcer dyspepsia.

There is a strong correlation between *H. pylori* infection and gastritis in both groups, confirming the findings of other workers (Warren & Marshall, 1983, Dixon, 1989).

Of the other factors studied, Cola nut ingestion is the only one that reaches a statistically significant difference (p<0.05), almost certainly due to advice given to patients with dyspepsia to stop eating Cola nut (Ibu, et al, 1986). The same advice probably explains the slightly lower intake of alcohol and lower level of smoking in dyspeptics.

There is a preponderance of males amongst those who volunteered, this is due to local cultural factors. There are no other differences which reach statistical significance, although the patients with dyspepsia have a higher prevalence of parasitic infestation and macroscopic pathology visible on endoscopy; specifically duodenitis, erosions, body gastritis, and polyps. Previous reports, discussed in chapter 2, suggests that duodenitis may be part of the...
spectrum of peptic-acid disease and as such may cause symptoms.

Eighty percent of this group (asymptomatic volunteers in northern Nigeria) are infected by *H. pylori*, not significantly different from the level of infection in those with non-ulcer dyspepsia (87%). However if this group is compared with similar asymptomatic groups in the 'West' the results are strikingly different (see figure 32).

**Fig.32.** Gastritis and *H. pylori* infection in the normal population: endoscopic studies.

In 10 endoscopic studies of asymptomatic volunteers of similar age in 'Western' populations (see literature review) the highest prevalence of gastritis is 53% (with a mean of 41%) and the highest prevalence of *H. pylori* infection is 41% (with a mean of 27%).

Such a high prevalence of gastritis and infection in a young, asymptomatic population calls in to doubt the pathological role of *H. pylori*. If it has any role at all in the cause of upper gastrointestinal pathology it can be only as a player in combination with other as yet undetermined factors.
CONCLUSION

This study does not provide any evidence to support an aetiologi-
cal role for *H. pylori* in the cause of non-ulcer dyspepsia. While the preceding
studies give little support for an aetiological role for *H. pylori* in non-ulcer dys­
pepsia, it is still possible that *H. pylori* does act in concert with other factors. If
this is the case clearance of *H. pylori* should lead to the resolution of symptoms
and assessment of this is the aim of the fourth and final study.
CHAPTER 7

THERAPEUTIC TRIAL OF HELICOBACTER PYLORI CLEARANCE
INTRODUCTION

Despite the high prevalence of *H. pylori* infection in the normal population it is possible that in patients with non-ulcer dyspepsia a second factor is present which interacts with *H. pylori* to cause symptoms, if this is the case clearance of the organism should relieve these symptoms.

METHODS

Patient selection, endoscopy, biopsy and diagnosis of *H. pylori* infection and histological gastritis is detailed in chapter 4 (pg 96 ff).

**Therapy**

The standard treatment for non-ulcer dyspepsia in northern Nigeria is with simple antacids, one such that is readily available, and commonly used is Gelusil (Warner Lambert). This is a combination of Magnesium Trisilicate 500mg and Aluminium Hydroxide 250mgs in each tablet, with a neutralizing capacity of 11.2 mEq./tablet.

It was decided to compare this standard treatment with an anti-*H. pylori* therapeutic combination, ie. tripotassium dicitratobismuthate (De Nol, Tabs Gist Brocades) 240 mgs four times daily for 28 days, together with amoxycillin 500mgs four times daily for the first 14 days.

**Randomisation and Blinding**

Each patient was randomly assigned to one of the two treatment groups using a table of random number. It was assumed at the outset of the trial, that *H. pylori* might be cleared in approximately 50% of the patients given bismuth & amoxycillin, therefore randomisation was carried out on a three to one basis in favour of bismuth and amoxycillin in order to obtain a large enough group of patients in whom *H. pylori* was cleared. The trial was investigator blind; the assessor was unaware of the *H. pylori* status or treatment the patient had
been given. Compliance was assessed at follow up by asking each patient how many, if any, tablets remained. Any patients with more than 20 tablets remaining were eliminated from the final analysis.

**Symptom Scoring**

Symptoms were scored as detailed in chapter 2. At follow up patients were re-scored with the addition of a further score reflecting global improvement or deterioration (see table 25). During the pilot study a linear analogue scale was used, but patients were unable to understand this and the simple global score detailed below was therefore used.

**Table 25: Global Scoring at Follow Up**

<table>
<thead>
<tr>
<th></th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Much Better</td>
<td>-10</td>
</tr>
<tr>
<td>Better</td>
<td>-5</td>
</tr>
<tr>
<td>Same</td>
<td>0</td>
</tr>
<tr>
<td>Worse</td>
<td>+5</td>
</tr>
<tr>
<td>Much Worse</td>
<td>+10</td>
</tr>
</tbody>
</table>

Non-ulcer dyspepsia is by definition a subjective feeling complained of by the patient. In an attempt to make assessment as objective as possible, complete resolution of symptoms at one month follow up, was chosen as the principle criterion of response and the more subjective measure of symptom score was used only as the subsidiary criterion of response.

The patients were followed up at one month (at the end of treatment) and two months by clinical assessment, symptom scoring, endoscopy and biopsy. The patients who had been randomised to Gelusil did not have a third endoscopy.

**Analysis**

Initial analysis was between the two treatment groups ie. Gelusil versus bismuth & amoxycillin. Ideally this would have been done on the basis
of intention to treat, however this was not possible due to the numbers who did not attend for follow up, and whose outcome could not be determined.

Following initial analysis between the Gelusil and bismuth & amoxycillin groups, the effect of _H. pylori_ clearance (defined as absence of _H. pylori_ on histological examination of two gastric biopsies taken at the end of treatment) on symptoms was assessed.

**Statistical Analysis**

The Chi squared test was used with the Yates correction where necessary, for comparison of the baseline data and the difference in symptom resolution. The improvement in symptom score was calculated for each patient and Students t-test used to compare the two groups. Confidence limits were calculated for the mean of the symptoms scores and for the difference in percentages.

**Trial Size: Power**

Using the principle response criteria defined as resolution of symptoms at one month follow up, the number of patients needed can be calculated using the following formula:

\[
 n = \frac{p_1 \times (100 - p_1) + p_2 \times (100 - p_2) \times f(\alpha, \beta)}{(p_2 - p_1)^2}
\]

Where: \( p_1 \) is the percentage of patients in whom symptoms might be expected to resolve when _H. pylori_ was not cleared and \( p_2 \) is the percentage of patients in whom symptoms resolve when _H. pylori_ was cleared. \( \alpha \) is the level of the Chi squared significance test used for detecting a treatment difference, in this case set at 0.05. \( 1 - \beta \) is the degree of certainty that the difference \( p_1 - p_2 \) if present, would be detected. In this case set at 0.90. \( \alpha \), commonly called the type I error, is the probability of detecting a 'significant
difference' when the treatments are really equally effective (ie. it represents the risk of a false-positive). $\beta$, commonly called the type II error, is the probability of not detecting a significant difference when there really is a difference of magnitude $p_1 - p_2$ (ie. it represents the risk of a false-negative result). $1 - \beta$ is called the power to detect a difference of magnitude $p_1 - p_2$.

For this study it was decided that symptoms might resolve in 20% of patients in whom $H. pylori$ was not cleared and that it would be reasonable to expect that symptoms might resolve in 50% of patients in whom $H. pylori$ was cleared. Using the above formula $n = 48$. Therefore to be able to detect a real difference of 30% between those who remain $H. pylori$ positive and those in whom $H. pylori$ has been cleared 48 patients are required in each group.
RESULTS

One hundred and thirty patients fulfilled the trial entry criteria and were randomised to either Gelusil (n=32) or bismuth & amoxycillin (n=98).

Table 26: Baseline Assessment: Therapeutic Trial

<table>
<thead>
<tr>
<th></th>
<th>Gelusil</th>
<th>Bismuth &amp; amoxycillin</th>
<th>$\chi^2$</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>32</td>
<td>98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male:</td>
<td>12</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>20</td>
<td>51</td>
<td>1.064</td>
<td>&gt;0.1 ns</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>26 yrs</td>
<td>28.6 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>24.5 yrs</td>
<td>27 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>13-47</td>
<td>14-67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>1 (3%)</td>
<td>1 (1%)</td>
<td>0.523</td>
<td>&gt;0.1 ns</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7 (22%)</td>
<td>16 (16%)</td>
<td>0.557</td>
<td>&gt;0.1 ns</td>
</tr>
<tr>
<td>Cola Nut</td>
<td>12 (37.5%)</td>
<td>31 (31.6%)</td>
<td>0.375</td>
<td>&gt;0.5 ns</td>
</tr>
<tr>
<td>Symptom Score</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>32</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% Conf.Limit</td>
<td>28.7 to 35.3</td>
<td>27 to 31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>33</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>14-47</td>
<td>6-47</td>
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<td></td>
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<tr>
<td>Macroscopic Findings on Endoscopy</td>
<td></td>
<td></td>
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<tr>
<td>Normal</td>
<td>19</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antral Gastritis</td>
<td>3</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duodenitis</td>
<td>6</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Gastritis</td>
<td>-</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary Reflux</td>
<td>-</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>2</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyp</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hiatus Hernia</td>
<td>-</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosions</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>14 lesions in 13 patients</td>
<td>45 lesions in 36 patients</td>
<td>0.034</td>
<td>&gt;0.5 ns</td>
</tr>
<tr>
<td>Macroscopic Pathology</td>
<td>13 (40.6%)</td>
<td>36 (38%)</td>
<td>0.035</td>
<td>&gt;0.5 ns</td>
</tr>
</tbody>
</table>
THERAPEUTIC RESPONSE:
One hundred and nine patients were re-assessed after the end of treatment. Of the 32 patients given Gelusil 9 failed to attend for follow up at one month leaving 23 (72%) patients for assessment. Of the 98 patients given bismuth and amoxycillin 12 failed to attend for follow up at one month, leaving 86 (88%) patients for assessment.

Table 27: Principle Criterion of Response: Symptom Resolution at 1 month follow-up (see figure 33)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Gelusil</th>
<th>Bismuth &amp; Amoxycillin</th>
<th>$\chi^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>86</td>
<td>7.39 $p&lt;0.01$</td>
</tr>
<tr>
<td>Symptom Resolution (%) at 1 month</td>
<td>1 (4.4%)</td>
<td>28 (32.6%)</td>
<td></td>
</tr>
<tr>
<td>95% Conf.Limit for %</td>
<td>-4 to 12.8%</td>
<td>22.7 to 42.5%</td>
<td></td>
</tr>
</tbody>
</table>

Table 28: Subsidiary Criteria of Response: Symptom Score at 1 Month Follow Up (see figure 34)

<table>
<thead>
<tr>
<th>Treatment Group</th>
<th>Gelusil</th>
<th>Bismuth &amp; Amoxycillin</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>23</td>
<td>86</td>
<td>2.116 $p&lt;0.05$</td>
</tr>
<tr>
<td>Mean</td>
<td>25.8</td>
<td>11.1</td>
<td></td>
</tr>
<tr>
<td>% Improve</td>
<td>20.6%</td>
<td>62.3%</td>
<td></td>
</tr>
<tr>
<td>95% Conf.Lim</td>
<td>4.1 to 37.1%</td>
<td>52.1 to 72.5%</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>23</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>% Improve</td>
<td>23.3%</td>
<td>70%</td>
<td></td>
</tr>
<tr>
<td>95% Conf.Limit %</td>
<td>6 to 40.6%</td>
<td>60.3 to 79.7%</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-53</td>
<td>0-43</td>
<td></td>
</tr>
</tbody>
</table>
Seventy one patients were re-assessed at their two month follow-up appointment (Gelusil n=16, bismuth & amoxycillin n=55). Symptom resolution occurred in 4/16 (25%; 95% confidence limits 7-43%) of those who had taken Gelusil and 22/55 (40%; 95% confidence limits 30-50%) of those who had taken bismuth & amoxycillin (see figure 33)(χ²; 1.202, p<0.5 n.s.). Symptom score at 2 months follow-up is shown in figure 34.
Table 29: Effect of Treatment on *H. pylori* Infection as assessed at one month follow-up (see figure 35)

<table>
<thead>
<tr>
<th></th>
<th>Gelusil</th>
<th>Bismuth &amp; Amoxycillin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number</strong></td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td><strong>Hp +ve e +ve</strong></td>
<td>17</td>
<td>32</td>
</tr>
<tr>
<td><strong>Hp +ve e -ve</strong></td>
<td>0</td>
<td>29 (7 of 18 with follow up at two months remained negative)</td>
</tr>
<tr>
<td><strong>Hp -ve e -ve</strong></td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td><strong>Hp -ve e +ve</strong></td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>No follow up</strong></td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td><strong>Unable to assess</strong></td>
<td>1</td>
<td>8</td>
</tr>
</tbody>
</table>

*H. pylori* was not cleared (see footnote) in any patients who had received Gelusil. *H. pylori* was cleared in 29 of 61 (48%) patients, who were originally infected and could be assessed at the one month follow up, who had taken bismuth and amoxycillin. Of the 29 patients in whom *H. pylori* was cleared 18 had a third gastroscopy, of which 7 remained negative for *H. pylori* and in 11 the organism had recrudesced. This gives an eradication (see footnote) rate (as opposed to clearance) of 7/50 (14%) (see figure 35).

**Comment**

Symptom resolution occurred in a significantly greater number of patients on bismuth & amoxycillin than on Gelusil (p<0.01). However bismuth is a complex compound and it may be that effects other than those acting specifically against *H. pylori* were responsible for the improvement in symptoms. It is important therefore to relate these findings to *H. pylori* clearance and eradication.

**FOOTNOTE:** *H. pylori* clearance was defined as the inability to detect *H. pylori* in histological sections at the end of treatment, in patients in whom *H. pylori* had been detected before treatment.

*H. pylori* eradication was defined as the inability to detect *H. pylori* in histological sections at least one month after the end of treatment, in patients in whom *H. pylori* had been detected before treatment.
*H. pylori* infection was diagnosed by histological examination gastric biopsies. In the assessment of *H. pylori* status the following patients had to be excluded: those who were *H. pylori* negative at entry into the trial (8), those in whom gastric biopsies at entry and follow up were not comparable (8) and those who failed to attend for their second endoscopy (9). This leaves 61 patients for assessment. Of these patients *H. pylori* was cleared in 29.

**Table 30:** Baseline Comparison of Patients: taking bismuth & amoxycillin according to *H. pylori* status at entry and one month follow up

<table>
<thead>
<tr>
<th><em>H. pylori</em> Status</th>
<th>Bi. Hp+ve e -ve</th>
<th>Bi Hp+ve e +ve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>(n=29)</td>
<td>(n=32)</td>
</tr>
<tr>
<td>Sex Male (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>13 (45%)</td>
<td>18 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Age: Mean</td>
<td>29</td>
<td>30</td>
</tr>
<tr>
<td>Median</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Range</td>
<td>18-67</td>
<td>16-65</td>
</tr>
<tr>
<td>Smoking</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Alcohol</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>NSAIDs (%)</td>
<td>2 (7%)</td>
<td>4 (13%)</td>
</tr>
<tr>
<td>Cola Nut (%)</td>
<td>8 (28%)</td>
<td>9 (28%)</td>
</tr>
<tr>
<td>Symptom Score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>30</td>
<td>28</td>
</tr>
<tr>
<td>95% Conf.Limit</td>
<td>26.1 to 33.9</td>
<td>24.7 to 31.3</td>
</tr>
<tr>
<td>Median</td>
<td>31</td>
<td>26.5</td>
</tr>
<tr>
<td>Range</td>
<td>6-47</td>
<td>10-43</td>
</tr>
<tr>
<td>Macrosopic Findings on Endoscopy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NAD</td>
<td>16</td>
<td>20</td>
</tr>
<tr>
<td>Antral</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastritis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Duodenitis</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Body gastritis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Biliary reflux</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Polyp</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Hiatus hernia</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Erosions</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Deformed bulb</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Total (%)</td>
<td>16 lesions in 13 pts. (45%)</td>
<td>16 lesions in 12 pts. (38%)</td>
</tr>
</tbody>
</table>

\[\chi^2: 0.723 \text{ p}<0.5 \text{ ns}\]
### Table 31: Primary Criterion of Response: Symptom Resolution according to H.pylori status (see figure 36)

<table>
<thead>
<tr>
<th>H.pylori Status</th>
<th>+ve -ve</th>
<th>+ve +ve</th>
<th>( \chi^2 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>29</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Symptom Resolution (%)</td>
<td>11</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Limits %</td>
<td>20.3 to 55.7%</td>
<td>12.4 to 43.6%</td>
<td></td>
</tr>
</tbody>
</table>

### Table 32: Subsidiary Criterion of Response: Symptom Score according to H.pylori status (see figure 37)

<table>
<thead>
<tr>
<th>H.pylori status</th>
<th>+ve -ve</th>
<th>+ve +ve</th>
<th>t</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>29</td>
<td>32</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>10</td>
<td>10</td>
<td>0.379 p&gt;0.5 ns</td>
</tr>
<tr>
<td>% Improvement</td>
<td>65%</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Limit %</td>
<td>47.6 to 82.4%</td>
<td>48.5 to 81.5%</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>7</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>% Improvement</td>
<td>76.7%</td>
<td>71.7%</td>
<td></td>
</tr>
<tr>
<td>95% Confidence Limit %</td>
<td>61.3 to 92.6%</td>
<td>56.1 to 87.3%</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>0-34</td>
<td>0-43</td>
<td></td>
</tr>
</tbody>
</table>

**Fig.35.** Change in H.pylori status in patients treated with Gelusil and bismuth & amoxycillin.

**GELUSIL n = 32**

**BISMUTH & AMOXYCILLIN n = 98**
**Therapeutic Response at Two Months**

Only 44 patients who had taken bismuth & amoxycillin had three endoscopies and the number of patients remaining is too small for statistical analysis. However symptom resolution was similar in patients in whom \textit{H. pylori} was eradicated (3/7), patients in whom \textit{H. pylori} infection had recrudesced (4/11), or patients who had remained infected by \textit{H. pylori} throughout the trial (14/26).
DISCUSSION

Therapeutic Response

Bismuth & amoxycillin is significantly better at resolving symptoms than Gelusil. Symptom resolution occurred in 28 of 86 patients given bismuth & amoxycillin, but in only 1 of 23 patients given Gelusil ($\chi^2$: 7.39, $p<0.01$). However the resolution of symptoms was not related to clearance of \textit{H. pylori}; symptoms resolved in 11 of 29 patients in whom \textit{H. pylori} was cleared and in 9 of 32 in whom \textit{H. pylori} was not cleared ($\chi^2$: 0.663, $p<0.5$, ns).

At the two month follow up bismuth & amoxycillin is still better than Gelusil at achieving resolution of symptoms, but due to the smaller numbers this does not reach statistical significance ($\chi^2$: 1.202, $p<0.5$, ns).

It is not possible to rule out some placebo effect contributing to the improvement of symptoms in the bismuth & amoxycillin group. Gelusil as the standard treatment in this environment had already been taken by many of the patients, whereas bismuth & amoxycillin was a new treatment which may have been thought by the patients to be more effective. However the improvement might also be due to a genuine therapeutic action of bismuth and/or amoxycillin, independent of its anti-\textit{H. pylori} effect.

Ideally the trial should have been double blind, however as Pounder and Nwokole (1990) point out this is all but impossible as bismuth colours the stools, and the need for antibiotics necessitates such a complex treatment regime that compliance would be compromised. This trial was investigator blind. All those treating and evaluating patients were unaware of the treatment or the \textit{H. pylori} status of the patient.
Pounder and Nwokolo (1990) also emphasise the necessity of a 'hard' end point, this is difficult in a subjective condition such as non-ulcer dyspepsia, but the use of complete resolution of symptoms at least approximates to this ideal.

The trials of anti-*H. pylori* treatment reported in the literature give conflicting results (see literature review). Only the trial of McNulty, et al (1986) and Lambert, et al (1989) show improvement in symptoms related to *H. pylori* clearance, and that reported by McNulty does not reach statistical significance. Several authors have reported an improvement in symptoms, but without relating this to bacterial clearance. Loffeld, et al (1989) did not find any improvement in symptoms in those taking bismuth over and above placebo. All the trials have been in relatively small numbers of patients.

Bismuth is an active compound with a cytoprotective action in its own right, and it may be that it is this, rather than the anti-*H. pylori* effect, which is responsible for the improvement in symptoms. A further double blind placebo controlled trial of bismuth alone in the treatment of non-ulcer dyspepsia in this environment is warranted.

**Bacterial Clearance and Eradication**

The overall clearance and the eradication rates are disappointing, 48% and 14% respectively. This compares with figures of 90% and 40% reported by (Rauws & Tytgat, 1989) for a similar treatment regime. Infection often recrudescences after the end of treatment (Langenberg, et al, 1986), however with such a high prevalence of infection in the community in northern Nigeria the risk of re-infection after clearance must be very high. Reinfection has been demonstrated by Collins, et al (1990), in patients whose families had a high prevalence of *H. pylori* infection. A high prevalence of infection amongst family members is the norm in northern Nigeria and re-infection acquired from close family mem-
bers living in the extended family must be likely. This would require restriction
endonuclease DNA ‘fingerprinting’ on the live organism and follow up samples
to determine this. This worthwhile study would be difficult logistically. I was
able to send some live organisms to the UK. for typing, but a high proportion
were not viable on arrival.

*H. pylori* was not eradicated in any patients given Gelusil.

**Follow Up**

Twenty eight percent (9) of those given gelusil and 12% (12) of
those given bismuth & amoxycillin failed to attend for follow up; a common
problem in research carried out in the ‘Developing World’. If patients are better
they don’t bother to attend, and if they are not better, or worse, they will often
consult a different doctor or herbalist. The lack of a proper address system in
Maiduguri and the long distance some patients had travelled, meant that tracing
defaulters was not possible. Follow up was further compromised by damage to
the gastroscope, which had to be sent to the UK for repair, and led to the can­
cellation of follow up gastroscopies.

This trial falls short of the ideal and typifies both the problems
experienced in trials of *H. pylori* eradication in non-ulcer dyspepsia and the
problems encountered in the ‘Developing World’.

**CONCLUSION**

There is no evidence from this trial that *H. pylori* causes non-ulcer
dyspepsia, although these studies cannot rule out a role for *H. pylori* in a particu­
lar subgroup of patients or a role in the cause of particular symptoms or a symp­
tom complex.
CHAPTER 8

DISCUSSION & CONCLUDING REMARKS
DISCUSSION AND CONCLUDING REMARKS

Helicobacter pylori is common amongst patients with non-ulcer dyspepsia; of 140 patients 120 (87%) were infected by \textit{H. pylori}, all of whom had histological gastritis, confirming in Africa, the pathological role of \textit{H. pylori} as the cause of type B antral gastritis. However there is no statistical difference between this high prevalence of infection and the prevalence of IgG antibodies to \textit{H. pylori} found in a random serological survey in which 228/268 (85%) of the population had antibodies to \textit{H. pylori}. These findings were confirmed in a group of 40 asymptomatic controls, 32 of whom (80%) had \textit{H. pylori} infection.

The majority of individuals in northern Nigeria have antibodies to \textit{H. pylori} and remain entirely asymptomatic.

\textit{H. pylori} is a difficult organism to eradicate; with a combination of bismuth & amoxycillin the organism was cleared in 29/61 (48%) at the end of therapy, but truly eradicated in only 7/50 (14%). However, although bismuth & amoxycillin was better at treating symptoms than Gelusil, this was not related to clearance or eradication of \textit{H. pylori}.

Bradford-Hill (1965) has described criteria to help judge if a factor is casual; the more criteria that are present, the more reasonable is the case for causality. The relationship between these criteria and \textit{H. pylori} in non-ulcer dyspepsia in northern Nigeria is summarised in table 33.
Table 33: Epidemiological criteria that suggest an association is casual
(Bradford-Hill, 1965)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>H. pylori &amp; non-ulcer dyspepsia in N. Nigeria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Strength of association</td>
<td>0</td>
</tr>
<tr>
<td>2. Specificity (an almost one to one relationship</td>
<td></td>
</tr>
<tr>
<td>between the association &amp; disease)</td>
<td>0</td>
</tr>
<tr>
<td>3. Appropriate time relationship</td>
<td>?</td>
</tr>
<tr>
<td>(association precedes disease)</td>
<td></td>
</tr>
<tr>
<td>4. Biological gradient (dose-response curve)</td>
<td>?</td>
</tr>
<tr>
<td>5. Biological plausibility</td>
<td>?</td>
</tr>
<tr>
<td>6. Coherence of the evidence</td>
<td>+/-</td>
</tr>
<tr>
<td>(data should not seriously conflict with known</td>
<td></td>
</tr>
<tr>
<td>facts relating to disease's history &amp; biology)</td>
<td></td>
</tr>
<tr>
<td>7. Experiment (disease is abolished or diminished</td>
<td></td>
</tr>
<tr>
<td>by removing the association)</td>
<td>0</td>
</tr>
</tbody>
</table>

+/-: Equivocal association, 0: no association, ?: no data available

As can be seen from table 33 the studies in this thesis do not provide any evidence that H. pylori causes non-ulcer dyspepsia in northern Nigeria, the hypothesis is thus disproved.

The Cause of Non-ulcer Dyspepsia in Northern Nigeria

It is likely that there is more than one pathology presenting with dyspepsia in this environment. Amongst the possible causes considered in the literature review duodenitis and parasitic infection were both more common in patients with non-ulcer dyspepsia than asymptomatic controls, and probably accounted for symptoms in some.

However this leaves three quarters of the patients (104 of 138)
without an apparent cause for their non-ulcer dyspepsia. A situation not
disimilar to that found in the 'West' where despite extensive research the cause
of non-ulcer dyspepsia in the majority of patients remains unknown. In Africa it
is difficult to justify extensive investigation of these patients in a disease with a
benign course, particularly when in the 'Developing World', resources and facili-
ties for investigation are limited and often unavailable.

Management of Dyspepsia in Northern Nigeria

The majority of patients with dyspepsia in northern Nigeria have
non-ulcer dyspepsia, those under the age of 40, in whom gastric cancer is
uncommon, should initially be treated with antacids, or indeed potash, as pre-
scribed by the traditional healers. While antacids are not of proven efficacy
over and above placebo, many patients will obtain symptomatic relief, and these
compounds are cheap and safe.

If dyspepsia persists, peptic ulcer and gastric cancer should be
excluded by barium meal or gastroscopy. Despite the difficulty in obtaining
these tests in many parts of northern Nigeria, every effort should be made, so
that unnecessary and often expensive treatment can be avoided. If peptic ulcer
is diagnosed, treatment with H2 blockers is appropriate.

However duodenal ulcer is a chronic relapsing condition, 80% of
patients will relapse within one year after healing with an H2 blocker (Kurata,
1988), while Marks, et al (1984), reported a recurrence rate of 46% even on
maintenance with H2 blockers in South Africa. Most patients cannot afford
repeat courses of H2 blockers and many live far away from the hospital so that
if their recurrent ulcer is heralded by perforation or a major upper
gastrointestinal bleed they are very likely to die before reaching hospital, and for
the endoscopically or barium meal proven recurrent ulcer a truncal vagotomy
and drainage: a relatively simple operation with a low mortality and 7% five year recurrence rate (Emas, 1985) may be appropriate.

H2 blockers are expensive and without proven efficacy in non-ulcer dyspepsia, they should only be used in patients with proven peptic ulceration. Treatment and eradication of \textit{H. pylori} in this environment is wholly impractical. The organism is difficult to eradicate, the cost of treatment high, the re-infection rate is unknown, and the benefits dubious.

\textit{The Pathogenic Role of H. pylori}

\textbf{Peptic Ulceration}

There is strong evidence from the ‘West’ that \textit{H. pylori} plays a role in the aetiology of peptic ulceration. Particularly convincing is data showing a reduction in the rate of duodenal ulcer recurrence from 80% if \textit{H. pylori} infection remains, to under 14% if \textit{H. pylori} is eradicated (Borody, et al, 1988). Of the 153 patients with dyspepsia who were gastroscoped in this study, 14 either had an active peptic ulcer or stigmata of a peptic ulcer, all were infected by \textit{H. pylori}. However compared to the ‘West’, peptic ulceration is uncommon in northern Nigeria and the majority of patients with \textit{H. pylori} infection do not have a peptic ulcer.

There are several possible explanations for this apparent contradiction of a high prevalence of \textit{H. pylori} infection and yet a low incidence of peptic ulceration.

The cause of peptic ulcer is multifactorial; diet, increased acid, smoking, genetic influences, drug intake, pepsin levels and the efficacy of the mucous-bicarbonate layer, as well as \textit{H. pylori} infection have all been implicated (Brooks, et al, 1985). Certainly smoking and the ingestion of non-steroidal anti-inflammatory drugs is much less common, and the genetic make up of the
population is different.

Jayari, et al (1980) working in India have defined areas of high and low incidence of peptic ulcer and related this to the usual diet in these areas. They found some foods protected against peptic ulcer, while others were relatively ulcerogenic (Jayaraj, et al, 1980). Of those found to be protective millet (the staple food in north eastern Nigeria) and okara (ladies fingers) are commonly eaten. It may be that the diet in north eastern Nigeria is protective against peptic ulcer despite a high prevalence of \textit{H. pylori} infection. More detailed dietary studies are needed.

There is no data available on acid output or pepsin levels in northern Nigeria and further work is needed in these areas.

Yoshimura, et al (1990) have suggested that \textit{H. pylori} associated with peptic ulceration differs at the genomic level from those found in patients with asymptomatic gastritis. It may be that the \textit{H. pylori} that commonly infects people in northern Nigeria, is genetically different from species that cause infection in the 'West', thus accounting for the benign course of infection in Nigeria. This needs to be investigated by restriction endonuclease DNA analysis of \textit{H. pylori} species in asymptomatic subjects and patients with non-ulcer dyspepsia and peptic ulceration, and comparison made with patients typed in the 'West'. Facilities for this are not available in Nigeria, and so live cultures would have to be transported to the UK, which is difficult.

It may be that infection acquired at a young age as in Nigeria runs a more benign course (Graham, et al, 1989). In the 'West' the majority of children are not infected and infection is acquired in adult life, whereas in Nigeria 80% of the population have antibodies to \textit{H. pylori} before 10 years of age (Holcombe, et al, 1990).
Gastric Cancer

H. pylori infection causes gastritis, and is commonly associated with intestinal metaplasia. It has been suggested that these are precursors to malignant change and that as a cause of gastritis H. pylori infection predisposes to gastric cancer (Correa & Ruiz, 1989). Talley et al, (1990) have shown an increased risk of gastric cancer in those infected with H. pylori three times that of the normal population.

In northern Nigeria, despite a high prevalence of H. pylori infection there is a low incidence of gastric cancer which accounts for less than 3% of tumours seen over four years at the University of Maiduguri Teaching Hospital (Holcombe, et al, 1989), and less than 2% of tumours in Zaria (Cedeerquist and Attah, 1986).

Persistent chronic inflammation leads to intestinal metaplasia (Dixon, 1989), and the development of carcinoma frequently follows in the train of metaplasia. Intestinal metaplasia has frequently been associated with H. pylori infection, but in this series of mucosal biopsies from Nigeria, intestinal metaplasia was found in only (1%). Weir, et al, (1988) have also reported a low incidence of intestinal metaplasia in patients with H. pylori infection in Africa. There seems to be a different histological response to H. pylori infection in northern Nigeria, either because of a difference in the organism, the host, the age of acquisition of infection or other associated factors which act in concert with H. pylori. This different histological response may account for the low incidence of gastric cancer, despite a high prevalence of H. pylori infection.
CONCLUSION

Most of the population in north eastern Nigeria are infected with *H. pylori*. Particularly striking is the high level of infection in children, probably as a result of person to person spread in large extended families living with less than ideal standards of hygiene. Apart from causing histological gastritis *H. pylori* infection seems to have few if any untoward effects. In particular there is no evidence that *H. pylori* causes non-ulcer dyspepsia thus disproving the hypothesis put forward in this thesis. The reason for the benign course of infection in northern Nigeria compared to the "West" needs to be investigated further, but may be due to a genomic difference in the organism, a different host response to infection or a lack of environmental co-factors necessary for the organisms pathological action.
APPENDIX 1: STATEMENT OF ETHICS AND WORK DONE

Project design, and organisation were done entirely by me. I did approximately 85% of the gastroscopies, assisted by Dr C.Thom, Lecturer in the Department of Medicine, university of Maiduguri. Histological examination was done by Dr S.B. Lucas, Senior Lecturer in the Department of Histopathology at University College and Middlesex School of Medicine. The microbiological culture was done by Miss Umar and Mr Habila in the Microbiology Department at the University of Maiduguri Teaching Hospital. Design and organisation of the serological survey was done by me, the serum samples were taken by medical students, from the College of Medical Sciences of the University of Maiduguri and subsequently put onto filter paper and sent to the UK. by me. The enzyme linked immunosorbant assays were done by Dr D.M. Jones and Dr J. Eldridge at the Public Health Laboratory in Manchester.

The project was presented in detail to the research committees of the College of Medical Sciences of the University of Maiduguri and the University Senate. These bodies, as well as considering the viability of the project and eligibility for a grant, considered the ethical aspects of the project and found these to be satisfactory.

This thesis records the first random serological survey of Ig G antibodies to \textit{H.pylori} in Nigeria. There are no other papers published from Africa documenting the prevalence of \textit{H.pylori} infection and gastritis in non-ulcer dyspepsia. This thesis gives details of the first therapeutic trial of \textit{H.pylori} eradication in Africa and thus provides an original contribution to the practice of medicine.
APPENDIX 2: H. PYLORI: CULTURE TECHNIQUE

Culture was carried out by Miss H. Umar and Mr Habila, lecturers in the Department of Microbiology at the University of Maiduguri Teaching Hospital.

Gastric mucosal biopsies were transferred from the endoscopy room to the microbiology laboratory in normal saline. On arrival in the laboratory the biopsy was streaked onto blood agar containing Skirrow's medium (vancomycin, trimethoprim & polymyxin B), then smeared onto a slide which, after gram staining, was examined under the microscope for H. pylori. The biopsy was then embedded into a urea agar slope to test for the presence of urease.

The blood agar plate was then incubated at 37C in a microaerophilic environment, created using a gas pack and catalyst (Oxoid BR60), in an anaerobic gas jar, for 5 days. Following culture the morphology of the colonies was noted. Typically Helicobacter pylori formed small, round, grey, shiny colonies as previously described (Humphreys and O'Morain 1988), these were Gram stained and identified microscopically, further characterisation showed the organism to be urease, catalase and oxidase positive, confirming the species.
APPENDIX 3: ENZYME LINKED IMMUNOSORBANT ASSAY

The assay as detailed below was carried out by Dr J. Eldridge at the Public Health Laboratory in Manchester, under the guidance of the director, Dr D.M. Jones.

**Elution**

On arrival at the laboratory each of the 0.1 ml aliquots (absorbed on filter paper) was eluted overnight in 1 ml of normal saline, so achieving a 1 in 10 dilution of serum. 0.1 mls of serum from each patient was then absorbed with Campylobacter jejuni.

**Absorption with Campylobacter jejuni**

**Introduction**

Campylobacter jejuni (C.jejuni) infection occurs throughout the world but is particularly prevalent in the 'Developing World', Ani, et al (1988) found antibodies to C.jejuni in 37% of Nigerian children. Some of the surface antigens of *H.pylori*, in particular the flagella proteins, have epitopes in common with C.jejuni (Newell, 1987). As a consequence antibodies to C.jejuni will also bind to *H.pylori* antigens. Because of the likelihood of a high prevalence of antibody to C.jejuni in the population studied all sera were absorbed with C.jejuni, before testing for *H.pylori* antibodies.

**Method**

A suspension of C.jejuni, grown on blood agar, was made in normal saline, and the organisms killed by heating at 60°C for two hours, this was then spun down (five minutes at 13,000 rpm.) to give a pellet of 0.1 gms of wet cells. To this pellet was added 0.1 ml of the patients serum. The organisms were resuspended and left to absorb overnight at 20°C. The suspension was then re-spun (five minutes at 13,000rpm.), the supernatant removed and the
absorbed serum, tested for antibodies to H. pylori.

**Enzyme Linked Immunosorbant Assay (ELISA) Technique**

The indirect enzyme linked immunosorbent assay for the detection of H. pylori antibody is based on the method of Voller and de Savigny (1981) and was validated by Jones, et al (1986).

A whole cell antigen was prepared using H. pylori cultures from six different patients. A standard suspension of cells was made (McFarland tube 4). A Falcon microtest 111 plate was then coated with 100µl of antigen per well. The plates were kept at 4°C for 18 hours to allow the antigen to adsorb and then washed x4 in distilled water. Coated plates were prepared freshly for each batch of sera tested.

For testing the patients sera were diluted to 1/300 in Dolbeco phosphate saline with the addition of 0.05% Tween 20 (polyoxyethylene sorbitan mono-oleate) and 1% bovine serum albumin. The Tween and the bovine serum albumin are added to stop non-specific adsorption of antibody to antigen. 100µl of diluted serum was added to duplicate antigen wells and the plates incubated for 1 hour at 37°C.

Following washing 100µl of anti-human IgG (Sigma) conjugated to horse-radish peroxidase was added to all wells. This was allowed to react at room temperature for 1 hour. The plates were then rewarshed in distilled water.

The enzyme substrate O-phenylene-diamine with hydrogen peroxide was then added and allowed to react for thirty minutes at room temperature. The reaction was stopped with a drop of 2.5 M sulphuric acid. Absorbency readings were taken on a Titertek Multiskan Elisa reader, which produces a numerical optical density read out.
Controls

Three known positive and five known negative sera were included with each plate. Tests are regarded as acceptable if the readings of the positive and negative controls are correct and the positive/negative ratio is correct.
APPENDIX 4: ON STUDY FORMS

HELICOBACTER PYLORI STUDY: THERAPEUTIC TRIAL PROFORMA

DEMOGRAPHY

Name:

Address:

Date of first interview

Study number:

Unit number:

Sex:  Male 1  Female 2

Age:

Religion:  Islam 1  Christian 2  Other 3

Tribe  Hausa 1  Kanuri 2  Bura 3
  Fulani 4  Shuwa 5  Marghi 6
  Other 7  

Occupation  Student 1  Farmer 2  Housewife 3  Nurse 4  Trader 5  Cattleman 6  Off. Worker 7  Other 8

Household income/mth.  State amount

Level of education:  Nil 0  Primary 1  Secondary 2  Poly. 3  University 4

Marital status:  Married 1  Single 2  Divorced 3  Widowed 4

Number of wives:  State number
 leave blank if not applicable

Children:  State number (blank if n/a)

ENTRY AND EXCLUSION CRITERIA:  Tick those applicable

Epigastric pain at least 3 months duration, related to meals.

✓ one of:  Heartburn  Night waking  Antacid relief
  Exacerbation  Exacerbation  Postprandial
  food  hunger  bloating

Exclude if:  patient has taken any antiulcer drugs or antibiotics in the last month (except antacids), if no pain in the last month.
Any previous upper GI surgery, pregnancy or serious illness.
EPIGASTRIC PAIN : CHARACTERISATION

When did the patient first have pain ? [ ][ ][ ] 32-34
i.e length of history (In months)

How often does pain usually occur ? [ ][ ] 35-36
On how many days per month (28 for daily)

How long ago was last episode of pain ? [ ][ ][ ] 37-39
Number of days, 0 for today

How long does pain usually last ? [ ][ ][ ][ ] 40-43
Number of minutes, max.720 for all day

On how many days has patient had pain in last two weeks ? (00 for nil) [ ][ ] 44-45

On how many days has patient taken antacids in last two weeks ? (00 for nil) [ ][ ] 46-47

Does pain stop daily activity ? Yes 1 No 2 [ ] 48

Is pain exacerbated by hunger ? Yes 1 No 2 [ ] 49

Is pain made worse by eating ? Yes 1 No 2 [ ] 50

Any assoc. retrosternal pain ? Yes 1 No 2 [ ] 51

Any assoc. postprandial bloating ? Yes 1 No 2 [ ] 52

Does pain wake patient at night ? Yes 1 No 2 [ ] 53

Does pain radiate to back ? Yes 1 No 2 [ ] 54

Does pepper exacerbate pain ? Yes 1 No 2 [ ] 55

Pain relieved by milk/antacids ? Yes 1 No 2 [ ] 56

Epigastric tenderness ? Yes 1 No 2 [ ] 57

Total Symptom Score ? [ ][ ][ ] 58-60
AETIOLOGY

Does patient drink alcohol? Yes 1 No 2 [ ] 61

If Yes: Type: Beer 1 Spirits 2 Local 3 [ ] 62

Other 4 Leave blank if not applicable

Quantity in bottles of beer / week [ ][ ][ ] 63-65

Does patient smoke? No./wk. 00 for non-smoker [ ][ ] 66-67

Does patient take Cola nut? Yes 1 No 2 [ ] 68

Any NSAIDs in last month? Yes 1 No 2 [ ] 69

Does anyone in family have pain? Yes 1 No 2 [ ] 70

If yes what relationship? Parent 1 Child 2

Cousin 3 Aunt/Uncle 4 Grandparent 5

Nephew/Neice 6 Sibling 7 Other 8 [ ] 71

Leave blank if not applicable

Has pt. taken any other medication? Yes 1 No 2 [ ] 72

If Yes: H2 Blocker 1 Antacid 2 A [ ] 73

Gastrozepin 3 Native 4 B [ ] 74

Other 5 state__________C [ ] 75

Leave blank if not applicable
Endoscopy findings

**Oesophagus:**
- Normal 1
- Oesophagitis 2
- Erosions 3
- Carcinoma 4
- Other 5 state

**Body:**
- Normal 1
- Gastritis 2
- Ulcer 3
- Erosions 4
- Healed U 5
- Carcinoma 6
- Other 7 state

**Antrum:**
- Normal 1
- Gastritis 2
- Ulcer 3
- Erosions 4
- Healed U 5
- Carcinoma 6
- Other 7 state

**Pyloris:**
- Normal 1
- Inflamed 2
- Deformed 3
- Erosions 4
- Other 5 state

**Duodenum:**
- Normal 1
- Duodenitis 2
- Ulcer 3
- Erosions 4
- Healed U 5
- Other 6 state

**Histology:**
- Gastritis Yes 1
- No 2
- Cp status +ve 1
- -ve 2

**Urease test:**
- +ve 1
- -ve 2

**Cp culture:**
- +ve 1
- -ve 2

**Cp antibody titre:**
- [ ]: [ ] [ ] [ ] [ ] 92-95
Name: 
Follow up Number: [ ] 96
Date [ ][ ][ ][ ][ ][ ] 97-102
Has pain completely resolved? Yes 1 No 2 [ ] 103

IF PAIN HAS COMPLETELY RESOLVED LEAVE 104 - 124 BLANK
If no is pain: Much better 1 Better 2
Same 3 Worse 3
Much worse 4 [ ] 104

How long ago was last episode of pain? [ ][ ][ ][ ] 105-107
Number of days, 0 for today.

How long does pain usually last? [ ][ ][ ][ ][ ][ ] 108-111
Number of minutes, max. 720 for all day

On how many days has patient had pain in
last two weeks? [ ][ ][ ][ ] 112-113

On how many days has patient taken antacids
in last two weeks? [ ][ ][ ][ ] 114-115

Does pain stop daily activity? Yes 1 No 2 [ ] 116

Is pain exacerbated by hunger? Yes 1 No 2 [ ] 117

Is pain made worse by eating? Yes 1 No 2 [ ] 118

Any assoc. retrosternal pain? Yes 1 No 2 [ ] 119

Any assoc. postprandial bloating? Yes 1 No 2 [ ] 120

Does pain wake pt. at night? Yes 1 No 2 [ ] 121

Does pain radiate to back? Yes 1 No 2 [ ] 122

Does pepper exacerbate pain? Yes 1 No 2 [ ] 123

Pain relieved by milk/antacids? Yes 1 No 2 [ ] 124

Epigastric tenderness? Yes 1 No 2 [ ] 125

Total symptom score? [ ][ ][ ][ ][ ][ ] 126

How many tablets does the pat. have left? [ ][ ][ ][ ][ ] 127-129
**DYSPEPSIA: Community Survey**

Name: 

Date: 

Age: 5-10 11-20 21-30 
31-40 51-60 60+ 

Age: 

Sex: Male Female 

Religion: Islam Christian Other state 

Tribe: Hausa Kanuri Shuwa Koyam Badoyi Other state 

Has patient ever had epigastric pain? Yes No 

If yes how long ago was the last episode? Within last: 
1 day 1-7 days 
8-28 days 1-6 months 
7-12 months 1 year + 

Does the pain ever wake the patient at night? Yes No 

Has the patient ever taken any medication for this pain? Yes No 

If yes what was it? 
Tagamet (Cimetidine) 
Zantac (Ranitidine) 
Mist. Mag. Trisilicate 
Gelusil 
Native medication 
Other - please state 

Epigastric tenderness? Yes No 

Was this pain severe enough to stop normal daily activity? Yes No 

State any relieving factors for the pain 

Is the pain related to meals? Made worse? Made better? 
Yes No

Is the pain relieved by Antacids or milk? Yes No Don't know 

How long does the pain usually last? 
<1 hour 1-2 hours 
2-6 hours 6-12 hours 
12 hours + 

Scarification marks? Yes No
How often does patient have pain?
- Daily 3-6x/week
- 1-2x/week 1-3x/month
- 1-5x/6 months 1 / year
- <1 / year

In last one month how many episodes of pain has the patient had?
- 1-4 5-10 11-20
- 20-30 30+

In the last one month has the patient taken any antacids?
- >1/day 1/day
- 6-4/week 2-3/week
- 1/week 1/month

Any serious illness in past?
- Yes  No  If yes please state

Alcohol?
- Yes  No  Type?
  - Beer  Spirits
  - Local brew, state
  - other, please state

Smoking?
- Yes  No  How many cigarettes each day?
  - <1 / day 1-5/day
  - 6-10/day 11-20/day
  - 21-40/day >40/day

Is there one particular food that makes the pain worse? Please state

Has patient taken any painkillers?
In last:
- 1 week 2-4 weeks
- 4-12 weeks

Were these NSAIDs?
- Yes  No

Does patient chew tobacco?
- Yes  No

Does patient take Cola Nut?
- Yes  No

Does patient take snuff?
- Yes  No
APPENDIX 5: ACKNOWLEDGEMENTS

I would like to thank the following for their generous financial support:

The Stanley Thomas Johnson Foundation
The University of Maiduguri
The University of Maiduguri Teaching Hospital

I would like to thank the following without whose help the project would not have been possible:

Professor K. Hobbs, Academic Department of Surgery, Royal Free Hospital, London.
Dr Sebastian Lucas, Department of Histopathology, University College and Middlesex School of Medicine.
Dr D.M. Jones and Dr J. Eldridge, Public Health Laboratory, Manchester.
Miss H. Umar and Mr Habila, Department of Microbiology, University of Maiduguri.
The staff of the theatre, University of Maiduguri Teaching Hospital
Dr C. Thom and Dr A. Abba, Department of Medicine, University of Maiduguri.
Dr A. Mc Neill, Church of Christ in Nigeria, Rural Health Programme.
Dr P.B.T. Jones
Mr Mike Richards, Sir Alfred Mc Alpines International, Hooton, Cheshire.
Professor A. Shaper, Department of Epidemiology, Royal Free Hospital, London.
Mr. D. Llewellyn, Department of Medical Illustration, Llandough Hospital, Cardiff.
APPENDIX 6 PUBLICATIONS (See addendum on back cover for full papers)


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NON-ULCER DYSEPSIA IN NIGERIA: A CASE CONTROL STUDY

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Abstract

Non-ulcer dyspepsia is common in Africa, yet there is little data on its possible cause. In this study 40 patients with strictly defined non-ulcer dyspepsia were matched with 40 asymptomatic volunteers. Both groups were questioned concerning their intake of alcohol, Cola nut, non-steroidal anti-inflammatory drugs and smoking, they then underwent upper gastrointestinal endoscopy with mucosal biopsy of the gastric mucosa; these biopsies were examined for gastritis and Helicobacter pylori.

Ingestion of Cola nut was the only statistically significant difference between the two groups. A high prevalence of gastritis and H. pylori infection was found in both groups, suggesting that these factors are not important in the aetiology of non-ulcer dyspepsia in northern Nigeria.
Introduction

Non-ulcer dyspepsia is common throughout Africa. In a random community study 26% of adults in rural northern Nigeria had experienced dyspepsia in the preceding six months (Holcombe, et al, 1990) and in endoscopic studies in Africa 65-90% of patients presenting with dyspepsia do not have any detectable upper gastrointestinal pathology (Abebe, 1983, Stahel, et al, 1981).

Although common, the aetiology of non-ulcer dyspepsia is unknown. In a recent review Talley & Phillips (1988) consider fourteen possible causes. However these studies investigating the cause of non-ulcer dyspepsia have been done in the 'West' where disease patterns, lifestyle and environmental factors are markedly different from those found in the 'Developing World'.

This case control study of patients with non-ulcer dyspepsia and asymptomatic volunteers was done at the University of Maiduguri Teaching Hospital in north east Nigeria. Maiduguri is in the northern savannah, of West Africa, an area characterised by high temperatures, low rainfall and a predominantly Muslim population.
Methods

Definition of non-ulcer dyspepsia

Non-ulcer dyspepsia was defined according to the criteria of the dyspepsia working party (Colin-Jones, 1988), with the exception that patients in whom nausea and vomiting, or prominent 'gaseous symptoms', or in whom symptoms of gastro-oesophageal reflux were pre-eminent, were excluded. This is comparable to the categories of ulcer-like dyspepsia (Colin-Jones, 1988), and essential dyspepsia, as defined by Talley & Phillips (1988). In practice patients were recruited for the study if they fulfilled the following strict entry and exclusion criteria:

a) Entry Criteria: Patients who had chronic epigastric pain of at least three months duration plus two of the following: exacerbation or relief by meals, exacerbation by hunger, night waking, heartburn, relief of pain by antacids or milk, epigastric tenderness.

b) Exclusion Criteria: Patients who had taken antibiotics, bismuth containing compounds, or anti-ulcer drugs other than simple antacids in the previous month, those who were seriously ill, pregnant, or had undergone previous upper gastrointestinal surgery and those who had experienced less than four episodes of pain in the preceding two weeks. Those with other pathology which may have accounted for the dyspepsia eg. irritable bowel syndrome (diagnosed according to the criteria of Manning, et al, (1978) gall bladder disease, tropical pancreatitis.
Patient Recruitment

Patients were recruited from Maiduguri and Borno State. All patients presenting to the University of Maiduguri Teaching Hospital with dyspepsia were referred to one of the authors for further assessment and possible endoscopy.

Assessment

Following entry into the trial each patient answered a standard questionnaire, documenting basic demography, symptoms and possible aetiological factors, and had a stool sample examined for parasites. Patients then underwent upper gastrointestinal endoscopy, when mucosal biopsies were taken from the antrum (within 2 cms of the pylorus) and the gastric corpus. The biopsies were fixed in 10% formalin and processed to paraffin. After staining with haematoxylin and eosin the biopsies were examined for gastritis (according to the criteria of Whitehead (1972)) and Helicobacter pylori. One hundred and thirty eight patients were entered into the trial and formed a bank of patients with non-ulcer dyspepsia. Forty of whom were subsequently matched with forty asymptomatic controls (see below).

Controls

Asymptomatic healthy volunteers were recruited, from amongst hospital staff, medical students and acquaintances. Thirty naira (£1.50) was offered to those who participated. Great care was taken to
exclude anyone who had experienced any upper gastrointestinal pain or symptoms in the preceding two years, or anyone who had a past medical history of peptic ulcer, had been investigated for dyspepsia or took antacids.

These asymptomatic volunteers were investigated in the same way as the patients with non-ulcer dyspepsia; by standard questionnaire, stool culture, endoscopy and biopsy.

On the completion of the study each asymptomatic volunteer was matched with a patient with non-ulcer dyspepsia, chosen from the bank of 138 patients with non-ulcer dyspepsia (see above). Patients were matched for age, sex, religion, ethnic group and educational level. Matching was done entirely blind, without knowledge of interview, gastroscopy or histology results.

This study was approved by the University of Maiduguri Research and Ethics Committee.

**Statistical Analysis**

The Chi squared test with Yates correction was used to compare the two groups.
Results

There were forty patients in each group, 36 male and 4 female, 18 Muslims and 22 Christians, both groups had a mean age of 25 years, and in each group 36 were from northern tribes and 4 from southern tribes (see table 1).

There were no statistically significant differences between the groups, except in the consumption of Cola nut which was more common in asymptomatic volunteers (see table 2). Both groups had a high prevalence of histological gastritis and H. pylori infection.
Discussion

These two closely matched groups of patients with non-ulcer dyspepsia, and asymptomatic controls are remarkably similar. The only difference that reaches statistical significance is consumption of Cola nut (p<0.05), but this is almost certainly accounted for by advice given to patients with dyspepsia to stop taking Cola nut (Ibu, et al, 1986).

Alcohol consumption, smoking and non-steroidal anti-inflammatory drug ingestion are equally uncommon in both groups. This confirms work by Talley, et al (1988) who did not find an association between smoking, alcohol ingestion or aspirin ingestion and non-ulcer dyspepsia.

There was a little more macroscopic pathology seen on endoscopy in patients with non-ulcer dyspepsia, although this does not reach statistical significance.

Duodenitis is part of the spectrum of peptic ulcer disease (Lagarde & Spiro, 1984). Joffe (1982) has suggested that it represents the formation and/or healing stage of peptic ulceration, and as such probably accounts for symptoms in some of these patients.

Histological gastritis was common in both groups. The correlation between macroscopic gastritis seen at endoscopy and histological gastritis was poor. All those with macroscopic gastritis had this confirmed histologically, but histological gastritis was present in a further 67% of asymptomatic controls and 67% of patients
with non-ulcer dyspepsia in whom the gastric mucosa looked normal. This confirms the findings of Sauerbruch, et al. (1987) and others who found a poor correlation between histologically defined gastritis and endoscopic appearances.

The prevalence of gastritis amongst the asymptomatic volunteers is particularly high compared to figures from the 'West'. In endoscopic studies of asymptomatic volunteers, of a similar age, in 'Western' populations the prevalence of gastritis varies from 20% (Dooley, et al., 1989) to 55% (Kimura, 1972). There is a strong correlation between H. pylori infection and gastritis in both groups, confirming the findings of other workers (Warren & Marshall, 1983, Dixon, 1989).

Recently H. pylori has been suggested as a possible cause of non-ulcer dyspepsia (Rokkas, et al., 1987), and there is a high level of infection amongst patients in this study with non-ulcer dyspepsia. However, there is no statistically significant difference between the level of infection between the cases and controls and this study highlights the importance of controls matched for age and ethnic group. In the 'West' H. pylori infection is present in 13-41% (Rokkas, et al., 1987, Flejou, et al., 1987) of asymptomatic volunteers, strikingly different from the 80% found in this group of asymptomatic controls.

The prevalence of parasitic infestation is higher in the patients with non-ulcer dyspepsia, although this difference does not reach statistical significance. Parasitic infestation has been suggested as a cause of epigastric pain and dyspepsia (Archampong,
Hookworm infection is said to be invariably associated with epigastric pain (Miller, 1979). Abdominal pain has also been reported with infestation of Taenia, Ascaris lumbricoides, Giardia duodenalis and Entamoeba histolytica (Soulsby, 1975, Meyer & Badulescu, 1978, Elsdon-Drew, 1968). However both parasitic infestation and dyspepsia are common and an association does not necessarily mean a causal relationship.

Patients with duodenitis will benefit from treatment with H2 blockers, while those with parasitic infestation should have this treated. For the remainder antacids are safe, cheap and give good relief of symptoms in many.
Conclusion

The cause of symptoms in this group of patients with non-ulcer dyspepsia from northern Nigeria remains unknown. Parasitic infestation and duodenitis probably account for symptoms in some, but H. pylori infection, gastritis, smoking, alcohol and non-steroidal anti-inflammatory ingestion seem unimportant in this environment.
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### Table 1: Baseline Data

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic Controls (40)</th>
<th>Cases (40)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex:</strong></td>
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Table 2: Comparison of Patients with Non-ulcer Dyspepsia and Asymptomatic Controls

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<th>Patients (n=40)</th>
<th>$\chi^2$</th>
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<tr>
<td>Alcohol</td>
<td>6 (15%)</td>
<td>2 (5%)</td>
<td>1.335 p&lt;0.5 ns</td>
</tr>
<tr>
<td>Cola Nut</td>
<td>26 (65%)</td>
<td>13 (30%)</td>
<td>5.075 p&lt;0.05 ns</td>
</tr>
<tr>
<td>Smoking</td>
<td>6 (15%)</td>
<td>2 (5%)</td>
<td>1.335 p&lt;0.5 ns</td>
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<tr>
<td>NSAIDs</td>
<td>3 (8%)</td>
<td>5 (13%)</td>
<td>0.881 p&gt;0.5 ns</td>
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</tbody>
</table>

| Endoscopy Findings:     |                               |                 |           |
|-------------------------|                               |                 |           |
| Antral gastritis        | 8 (20%)                       | 9 (23%)         |           |
| Biliary reflux          | 2 (5%)                        | 1 (2.5%)        |           |
| Oesophagitis            | 1 (2.5%)                      | 1 (2.5%)        |           |
| Duodenitis              | 1 (2.5%)                      | 5 (12.5%)       |           |
| Gastric Body erosion    | -                             | 3 (7.5%)        |           |
| Gastritis of Body       | -                             | 2 (5%)          |           |
| Polyp                   | -                             | 2 (5%)          |           |

| Histological Findings   |                               |                 |           |
|-------------------------|                               |                 |           |
| Histological Gastritis  | 35 (87.5%)                    | 36 (90%)        | 0.125 p>0.5 ns |
| H.pylori infection      | 32 (80%)                      | 35 (87.5%)      | 0.367 p>0.5 ns |

| Parasites               |                               |                 |           |
|-------------------------|                               |                 |           |
| Entamoeba histolytica   | 2/16 (12.5%)                  | 4/23 (17%)      |           |
| Schistosoma mansoni     | 1/16 (6%)                     | 1/23 (4%)       |           |
| Hookworm                | -                             | 2/23 (9%)       |           |
THE PREVALENCE OF SYMPTOMS OF DYSPEPSIA IN NORTH EASTERN NIGERIA:
A RANDOM COMMUNITY BASED SURVEY

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UNIVERSITY OF MAIDUGURI TEACHING HOSPITAL, NIGERIA.

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Department of Surgery,
Charing Cross Hospital,
London W6
ABSTRACT

In a randomised household survey of 620 people in rural north eastern Nigeria there was a 26% six month prevalence of dyspepsia in adults and a 6% prevalence amongst teenagers. Dyspepsia was associated with the intake of alcohol (p<0.0054) and Cola nut (p<0.00013). The prevalence increased with age; the mean length of history was nearly four years and over half of the subjects with dyspepsia had sought medical advice, mainly from traditional healers.

12% of a similar group of hospital patients with dyspepsia were previously found to have peptic ulceration, suggesting that the community prevalence for peptic ulceration is 18/1000. This is lower than found in the 'West'.

INTRODUCTION

Dyspepsia is common worldwide, accounting for enormous morbidity and cost to the health care system (1). The prevalence of dyspepsia in the 'Developing World' is poorly documented and there have been very few population based, random studies to assess the true prevalence. Similarly the data on peptic ulceration is scarce and often gathered from secondary sources mainly those presenting to hospital with complications; this must inevitably give an underestimate of the prevalence. Knowing the prevalence of dyspepsia in the community and the proportion who are likely to have peptic ulceration, it is possible to estimate the true prevalence of peptic ulceration in the community.
METHODS

Definition of Dyspepsia

Dyspepsia was defined as epigastric pain related to meals and/or exacerbated by hunger. Subjects were also questioned about night waking, and relief by milk or antacids, and examined for epigastric tenderness. This definition is equivalent to the 'ulcer-like dyspepsia' category of non-ulcer dyspepsia as defined by the management of dyspepsia working party (2).

Interview Technique

Five separate rural villages close to the state capital Maiduguri were surveyed. Houses in these villages had been previously numbered in preparation for the primary health care scheme. Households to be interviewed were randomly selected using a table of random numbers. Occupants over five years of age were interviewed by medical students with the help of village health workers as interpreters, using a questionnaire, previously validated in a pilot study, documenting basic demography, dyspeptic symptoms, length of history and possible aetiological factors.

Statistical analysis was done using the Chi-squared test.
RESULTS

Six hundred and twenty subjects were interviewed, 345 males and 275 females, aged 5-80 with a mean age of 27 years. The age distribution of the sample is shown in figure 1, this is a typical age distribution for the 'Developing World', with half of the sample (320) aged less than 20. In this rural sample the commonest occupations were farming (34%) and that of a housewife (25%). The staple food was millet, which was eaten by 86%, small amounts of guinea corn and rice were also eaten. All the subjects were from northern Nigeria, mostly from the Kanuri ethnic group (81%).

DYSPEPSIA

Eighty (26%) adult subjects (over 20 years of age) had had dyspepsia in the last six months, a further 13 (4%) in the more distant past. 11 (6%) teenagers and 2 (2%) children aged 5-10 years had also had dyspepsia. There were 56 males and 37 females in this group. The length of history varied from one month to over ten years with a mean of almost four years (46 months). The prevalence of dyspepsia in this sample increased with age, although the numbers at the upper end of the age range are small (see figure 2).
Of the 93 subjects who had experienced pain, in 52 (55%) it was severe enough for them to have sought medical advice, this was usually from traditional healers, (35 subjects), who most often prescribed potash which generally gave the patients good temporary relief from their symptoms. In 37 (49%) the symptoms were severe enough to stop the subjects normal daily activity. The commonest exacerbating factor was hunger. The frequency of the pain varied markedly between subjects, but 87% had experienced pain at least once in the proceeding four weeks with 6% experiencing pain every day.

There was no difference in the type of food eaten, or occupations of those who did and did not have dyspepsia. Alcohol intake, Cola nut ingestion (a locally available stimulant containing caffeine), smoking and the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) were all more common in those with dyspepsia than those without (see table 1). However the association only reaches statistical significance in the case of alcohol (p<0.0054, odds ratio 2.50) and Cola nut ingestion (p<0.00013, odds ratio 2.85).
DISCUSSION

The most important finding was a six month prevalence of dyspepsia amongst adults in north east Nigeria of 26%. This represents a significant cause of morbidity, contrary to previous impressions (3) and is remarkably similar to that found in the 'West' where prevalence rates varying from 25–38% have been reported (4,5,6). A prevalence of 6% was found amongst teenagers a group not normally studied, but because of the age distribution of the population studied, constituting a large number of subjects.

Mengesha (7) found an incidence of dyspepsia of 17% in over 14,000 outpatients in Addis Ababa, and 4.8% of one and a half million patients presenting to health posts scattered throughout Ethiopia. However this survey only recorded those who had sought formal health care and is likely to be a considerable underestimation. This random study as well as others (4) have shown that many people never seek medical advice; those who do seek advice in this environment go to traditional healers and not to formally trained health workers. We know of no other random surveys of the prevalence of dyspepsia in Africa.
The percentage of the sample with dyspepsia increased with age reaching 100% over 60, (although the numbers over 60 are very small), (see figure 3), contrary to the findings of Jones and Lydeard (4) who found that the frequency of dyspepsia decreased with age. The traditional healers on the whole seem effective at treating dyspepsia, however the disadvantage of this is that those with more serious pathology will not be referred and will as a consequence be diagnosed late. As found in other studies in Africa (7,8,9) subjects had suffered with dyspepsia for a long time, with a mean of almost four years in this study.

Alcohol and Cola nut ingestion were both significantly associated with dyspepsia (see table 1). Cola nut is a locally available, mildly addictive stimulant with a high caffeine content, equivalent to coffee which has been implicated in the cause of non-ulcer dyspepsia (10). The alcohol that is drunk in this area is usually burukutu, fermented from sorghum and locally made gin, both of which have a high alcohol content. In this study no association has been shown between dyspepsia and smoking or non-steroidal anti-inflammatory drug ingestion.
The strict diagnosis used for dyspepsia in this study will exclude the majority of other pathologies which may present with dyspeptic like symptoms. Gall stones which would be a common differential diagnosis in the 'West' are rare in Africa (11) as is hiatus hernia and gastro-oesophageal reflux. Bassey et al (12) found an incidence of only 0.39% and 2.2% respectively in over 1,000 barium meals. Patients with tropical pancreatitis usually have steatorrhea and weight loss so can be diagnosed clinically (13).

Parasitic infestation was not excluded and this may be of importance (14). In observations of the incidence of epigastric pain and parasitic infestation presenting to six rural health centres in north east Nigeria the incidence of each varied with the season and were well correlated. The maximum incidence for both was in August, at the end of the wet season, 241 and 181 patients respectively, there was then a dramatic fall to only 38 patients with epigastric pain and 70 with parasites in December (McNeill, personal communication).

The cause of non-ulcer dyspepsia remains unknown. Recently Helicobacter pylori (H. pylori) has been implicated in the aetiology of non-ulcer dyspepsia (15). The prevalence of H. pylori in this area is much higher than in a population of similar age in the 'West' (16). The fact that the prevalence of dyspepsia is no higher than in the 'West' suggests that H. pylori is not the only factor involved in the aetiology.
Hyperacidity is unlikely to play a role in the cause of dyspepsia in this environment (17), while for this population no data is available on possible gastric dysmotility, which has also been suggested as a possible cause of non-ulcer dyspepsia (18). Stress (19) has often been cited as a cause of dyspepsia ever since observations by Beaumont (20) on his patient with a gastric fistula, Alexis St. Martin. Present day life in Nigeria is certainly stressful, but again no objective evidence exists for this population.

Tovey and Tunstall (3) reported that peptic ulceration is rare in Northern Nigeria, however this data was hospital based and dependent on numbers of inpatients, mostly those with the complications of peptic ulceration. This leads to serious under reporting as many patients with peptic ulcer in this environment will never seek formal medical care and many will never have complications from their ulcer.

In an endoscopy series of 57 patients with dyspepsia presenting to the University of Maiduguri Teaching Hospital, and using the same definition of dyspepsia as above, Holcombe et al (21) found 6 duodenal ulcers and 1 prepyloric gastric ulcer (12%). In this village survey 80 out of 300 adults had experienced dyspepsia in the previous six months, i.e. a six month prevalence rate of 26.6/1000. If a similar incidence of peptic ulcer can be assumed for these patients (i.e. 12%), then the prevalence rate for peptic ulcer is 32/1,000.
Jones and Lydaard (4) found that in their sample 73/1000 subjects had had a peptic ulcer diagnosed, more than double that found in the present study. So while the prevalence of dyspepsia is remarkably similar to that found in the 'West', the number of patients with peptic ulceration is less, suggesting that there are different pathologies involved and that non-ulcer dyspepsia and peptic ulcer disease are not different points on the continuum of acid related disease.

H. pylori is strongly associated with peptic ulcer (22) and has been implicated in its aetiology. With such a high prevalence of H. pylori infection (16) one might expect peptic ulcer to be more common here than in the 'West', the lower prevalence suggests that H. pylori is not the only factor involved in its aetiology. Cigarette smoking has been linked to changes in the incidence of peptic ulceration (23), the incidence of smoking and alcohol intake here is much lower that in the 'West' and it may be that it is a combination of these factors and H. pylori infection that is important in the aetiology of peptic ulceration.
CONCLUSION

Dyspepsia is a significant cause of morbidity in north eastern Nigeria. The cause is probably due to a combination of factors related to the individual, the environment and common infections. Alcohol and Cola nut ingestion are important environmental factors. Infection with parasites and H. pylori are common but their aetiological role is uncertain.

The prevalence of peptic ulceration is lower than in the 'West' and the high prevalence of H. pylori infection in this population suggests that this is not the sole factor causing peptic ulceration, but it may be important in combination with alcohol and smoking elsewhere.
REFERENCES


20 Beaumont, W.. Experiments and observations on the gastric juice and the physiology of digestion (facsimile of 1833 edition), Dover, New York, 1959; 107


ACKNOWLEDGEMENTS

We would like to thank the students of the College of Medical Sciences, University of Maiduguri for their help with this project. This work has been supported by grants from the Stanley Thomas Johnson Foundation, the University of Maiduguri and the University of Maiduguri Teaching Hospital.
Table 1: Relationship between dyspepsia and alcohol intake, smoking, non-steroidal anti-inflammatory drugs and Cola nut ingestion.

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<th>No Dyspepsia</th>
<th>Dyspepsia</th>
<th>p value</th>
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<tbody>
<tr>
<td>Alcohol</td>
<td>34/527 (6%)</td>
<td>14/93 (15%)</td>
<td>&lt;0.0054</td>
</tr>
<tr>
<td>Smoking</td>
<td>55/527 (10%)</td>
<td>10/93 (11%)</td>
<td>&lt;0.926 (ns)</td>
</tr>
<tr>
<td>NSAID Ingestion</td>
<td>139/527 (26%)</td>
<td>27/93 (29%)</td>
<td>&lt;0.593 (ns)</td>
</tr>
<tr>
<td>Cola nut Ingestion</td>
<td>322/527 (61%)</td>
<td>76/93 (82%)</td>
<td>&lt;0.00013</td>
</tr>
</tbody>
</table>

ns: not significant.
**Helicobacter (=Campylobacter) pylori in Africa**

C. Holcombe¹, S. B. Lucas⁴, H. Umar³ and A. Abba²  Departments of ¹Surgery, ²Medicine, and ³Microbiology, University of Maiduguri, Nigeria; ⁴Department of Histopathology, University College and Middlesex School of Medicine, London, UK

Abstract

Epigastric pain is a common complaint throughout Africa, mostly in the form of non-ulcer dyspepsia. It has recently been suggested that Helicobacter (=Campylobacter) pylori, a bacterium that colonizes the gastric mucosa and causes type B gastritis, may be the cause of this epigastric pain. This paper reports the endoscopic, histological and bacteriological findings in 57 patients presenting with epigastric pain to the University of Maiduguri teaching hospital during one year, together with a review of the African literature. Of 57 patients, 49 had non-ulcer dyspepsia, 7 peptic ulceration and 1 carcinoma of the stomach. The prevalence of gastritis and non-ulcer dyspepsia is not strong enough to be able to extrapolate throughout the continent.

Methods

The University of Maiduguri teaching hospital lies in the sahel of northern Nigeria, an area characterized by high temperatures and low rainfall.

In one year, from February 1988 to February 1989, 57 patients presenting with epigastric pain were examined. Patients were recruited for the study if they fulfilled the following entry criteria: epigastric pain related to meals, plus one of the following symptoms: night waking, heartburn, post-prandial bloating or relief of pain by antacids or milk. Patients who had taken antibiotics, or anti-ulcer drugs other than antacids, during the previous month were excluded, together with those who were pregnant or suffering from other serious illness.

A standard proforma was completed for each patient, who then underwent upper gastrointestinal endoscopy. Biopsy specimens were taken from the stomach, one from the body and 2 from the antrum. Two specimens were fixed in formalin; sections were stained with haematoxylin and eosin and Giemsa stains, and examined for the presence of helicobacter-like organisms and gastritis.

Some of the antral biopsy specimens were cultured. A piece of tissue was first streaked on to blood-agar, then smeared on to a slide which, after Gram-staining, was examined under the microscope for H. pylori. It was then embedded in a urea agar slope to test for the presence of urease. The blood-agar plate was incu-

bated at 37°C for 5 d in a microaerophilic atmosphere produced by means of a gas generating kit (Oxoid BR60) and catalyst in a closed jar. Typically, H. pylori formed small, round, grey, shiny colonies as previously described (HUMPHREYS & O'MORAIN, 1988). Identification was confirmed by microscopic morphology and positive urease, catalase and oxidase tests.

**Results**

57 patients were studied, 39 male and 18 female, with a mean age of 34 years and a mean length of history of 38 months (range 0.5–240 months). Most were from the tribes of northern Nigeria (58%), few drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%). The commonest exacerbating factors were hunger (35%) and drank alcohol (15%), smoked (13%) or took non-steroidal anti-inflammatory drugs (4%).

Histological examination showed that 53 (93%) of the 57 patients had gastritis, and of these 46 (87%) were also colonized with *H. pylori* (Table 1).

Culture was attempted in 21, all showing helicobacter-like organisms on histology, and was successful in 13.

**Discussion**

These results, from patients with epigastric pain, showed a high prevalence of gastritis (93%) and of colonization with *H. pylori*, which was present in all patients with peptic ulceration and 80% of those with non-ulcer dyspepsia. This compares with figures from Australia of 90% colonization in duodenal ulcer, 70% in gastric ulcer and 60% in non-ulcer dyspepsia (MARSCHALL et al., 1985a).

This high prevalence is seen throughout Africa. In studies from 5 African countries, all done on patients with epigastric pain, the prevalence of gastritis varied from 80–100%, and the percentage colonized with *H. pylori* varied from 75–97% (see Table 2).

There is strong evidence that *H. pylori* causes type B non-autoimmune gastritis. The organism is almost universally associated with the lesions (MCNULTY, 1987), it caused gastritis in 2 human volunteers (MARSHALL et al., 1985b; MORRIS & NICHOLSON, 1987), and its elimination leads to an improvement of gastritis (MCNULTY et al., 1986). Certainly the strong association between *H. pylori* and gastritis in Africa (Table 2) supports a causal role for it there.

In the western hemisphere the prevalence of *H. pylori* in the general population rises with age from 19% under 50 years to 50% over 50 years (WYATT et al., 1987a). The prevalence in patients with non-ulcer dyspepsia varies from 28% (BERSTAD et al., 1988) to 74% (LOFFELD et al., 1988). BORODY et al. (1987) also reported that symptoms of non-ulcer dyspepsa improved after elimination of *H. pylori*.

Whether *H. pylori* gastritis is related to non-ulcer dyspepsia is less clear. Its prevalence in non-ulcer dyspepsia patients in Africa varies from 69% (ROUROY et al., 1987) to 96% (WYATT et al., 1987b). However its prevalence in ‘normal’ African population is equally high. In the Ivory Coast 75% of the population (all ages) and 55% of children aged less than 10 years have antibodies to *H. pylori* (MÉGRAUD et al., 1989), and in Kenya 13 of 14 asymptomatic volunteers were found to have *H. pylori* and gastritis (LACHLAN et al., 1988). Yet in the latter study, in which symptomatic patients were also included, non-ulcer dyspepsia improved when *H. pylori* was eradicated.

In the western hemisphere there is a strong

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Gastritis</th>
<th>-Hp</th>
<th>-Hp</th>
<th>+Hp</th>
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<tr>
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<td>-</td>
<td>-</td>
<td>6 (10.5%)</td>
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<tr>
<td>Gastric ulcer</td>
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<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Carcinoma of stomach</td>
<td>1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1 (1.8%)</td>
</tr>
<tr>
<td>Total</td>
<td>46 (80.7%)</td>
<td>7 (13%)</td>
<td>3 (5.6%)</td>
<td>1 (1.9%)</td>
<td>57 (100%)</td>
</tr>
</tbody>
</table>

*Hp* = infected with *H. pylori.*

+Hp = not infected with *H. pylori.*

<table>
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<td>145</td>
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<td>(80%)</td>
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<td>38</td>
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<td>(85%)</td>
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<tr>
<td>Zimbabwe</td>
<td>46</td>
<td>145</td>
<td>38</td>
<td>(93%)</td>
<td>(85%)</td>
</tr>
</tbody>
</table>

*All studies on dyspeptic patients, except for one control study (see discussion).*
association between gastritis and peptic ulceration (SCHRAEGER et al., 1967); *H. pylori* and peptic ulceration are associated in 90% of patients (MARSHALL et al., 1985a). This association has been confirmed in Africa (LACHLAN et al., 1988; ROUVROY et al., 1987; WEIR et al., 1988; WYATT et al., 1987b), but a causal relationship is not proven (RATHBONE et al., 1988).

In Africa most patients with *H. pylori* do not have peptic ulceration (only 6 of 57 in the present study), so if *H. pylori* is implicated in the cause of peptic ulceration it must be in combination with other factors. This must apply particularly to gastric ulcer, which is uncommon in most of Africa (ABEBE, 1983).

How should the patient who presents with epigastric pain in Africa be treated? Ideally a definitive diagnosis should be made by either endoscopy or barium meal. A peptic ulcer can be effectively treated with a combination of drugs, e.g. amoxycillin and a bismuth compound such as tripotassium dicitratobismuthate (De-Nol®, Gist-Brocades) or bismuth subsalicylate (Proctor and Gamble?).

It seems unlikely that *H. pylori* gastritis is the only, or major, cause of non-ulcer dyspepsia in Africa, in view of the very high prevalence in the asymptomatic population found by LACHLAN et al. (1988) and MÉGRAUD et al. (1989). It is much more likely that *H. pylori* is only one factor involved in the aetiology. At present the routine use of anti-*H. pylori* drugs in Africans with non-ulcer dyspepsia cannot be recommended.

There is a need for further research. In particular the epidemiology of *H. pylori* needs to be established, both in the general population and in those with epigastric pain. Control studies are needed to establish the prevalence of gastritis in the asymptomatic population. The other aetiological factors causing non-ulcer dyspepsia need to be established, and finally one must await the results of randomized, controlled, therapeutic trials to determine the clinical effect of the elimination of *H. pylori*.

Acknowledgements

We are grateful for financial support for this study from the Stanley Thomas Johnson Foundation, the University of Maiduguri Teaching Hospital, and the University of Maiduguri. We are also grateful for the help of the theatre staff of the University of Maiduguri Teaching Hospital.

References


Received 28 July 1989; revised 12 October 1989; accepted for publication 19 October 1989.
Incidence of Duodenal ulcer in the northern savannah of Nigeria

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SUMMARY
In 4 years, 200 patients were admitted to the University of Maiduguri Teaching Hospital, in the Northern Savannah of Nigeria, with a clinical diagnosis of peptic ulcer; 60 had the diagnosis of duodenal ulcer confirmed on barium meal or at operation, giving an incidence of 6/1000 adult admissions (excluding obstetrics). There were no gastric ulcers.

Forty-four patients had a ‘simple ulcer’, 10 presented with gastric outlet obstruction, five with peritonitis following perforation and one with haematemesis. There were 44 males, and 16 females, with a mean age of 34 years and mean length of history of 44 months.

Contrary to previous published reports improved diagnostic facilities have shown duodenal ulcer to be relatively common in the Northern Savannah of West Africa.

INTRODUCTION
The incidence of peptic ulcer varies widely in different regions of Africa. Konstam first suggested in 1954 that peptic ulcer was rare in the dry, northern savannah of Nigeria, in contrast to the high incidence along the west coast of Africa; this was confirmed by Tovey and Tunstall in a comprehensive study of duodenal ulcer in black populations south of the Sahara. However this study was of hospital admissions, many of which did not have facilities for barium meal and the diagnosis of duodenal ulcer was therefore often dependent on surgery in those with complications.

In 1982 a new teaching hospital was opened in Maiduguri, in the northern savannah of Nigeria, allowing the reliable diagnosis of peptic ulcer by barium meal in those without complications. This study was carried out to reassess the incidence of admission for peptic ulcer, with and without complications, using these newly available diagnostic facilities.

METHODS
This study is a retrospective review of all patients admitted to the University of Maiduguri Teaching Hospital with a diagnosis of peptic ulcer, duodenal ulcer or gastric ulcer over 4 years (1984-1987).

The hospital has a good medical records department with well-trained staff. The hospital was planned as a tertiary referral centre for north east Nigeria, but medical facilities are limited in the rest of the region so a large proportion of patients are seen without prior referral. The patient population is however biased towards the better educated, town dwellers who have a little more money than is the norm for the whole region.

Diagnosis of peptic ulcer was made mainly on the basis of barium meal findings. These were done in a well equipped X-ray department by trained radiologists who also reported on the films.

RESULTS
Over 4 years 200 patients were admitted with a clinical diagnosis of duodenal or peptic ulcer: 60 had a duodenal ulcer confirmed by barium meal or at operation, 39 had a normal barium meal and in 101 no definite diagnosis was made; these were usually patients who were asked to attend for outpatient barium meal, but did not return for the X-ray or further follow up.

There were a total of 9883 adult admissions (excluding obstetrics) during the period of the study, giving an incidence of 6/1000 admissions for duodenal ulcer and 20/1000 for dyspepsia. It is notable that of 200 patients with a clinical diagnosis of duodenal ulcer this was confirmed in only 30%.

Of the 60 patients with duodenal ulcer, 16 (27%) presented with complications, 10 with gastric outlet obstruction (17%), five with perforation (8%) and one with haematemesis, a further 11 (18%) were operated on for failure of medical management. Of the remainder (33), 29 were treated with H2 blockers and four with antacids (Table 1).

The male to female ratio was 2.8:1 and the mean age was 34 years. Most patients (77%) were from northern tribes. The mean length of history was 44 months, ranging from those who had been asymptomatic before a sudden perforation, to those with a history of over 20 years. The commonest presenting complaint was epigastric pain and the
Table 1. Diagnosis and treatment in 60 patients with duodenal ulcer

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Total</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H2 block</td>
<td>Antacids</td>
</tr>
<tr>
<td>Simple ulcer</td>
<td>44</td>
<td>29</td>
</tr>
<tr>
<td>Gastric outlet</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Haematemesis</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>60</td>
<td>30</td>
</tr>
</tbody>
</table>

commonest sign epigastric tenderness. No particular occupation predominated. The commonest exacerbating factors were pepper and hunger.

Those in whom barium meal was normal and no other diagnosis could be found were given a diagnosis of non-ulcer dyspepsia. They were older with a mean age of 39 years. The length of history was shorter at 25 months and there were more females than males, with a male to female ratio of 1:1.3.

DISCUSSION
Duodenal ulcer accounts for 6/1000 admissions, an incidence considerably higher than that found by Tovey and Tunstall (<1/1000) in 1975. However in Tovey and Tunstall's series most patients had complications, a group accounting for 1.6/1000 admissions in this series. The improved diagnostic facilities have revealed a previously undiagnosed group of patients with uncomplicated duodenal ulcer.

There was a modest rise in the number of patients admitted with complications, suggesting there is also a true rise in the incidence of duodenal ulcer. This was due in part to 'southerners' migrating to the north (almost a quarter of the patients in this study), who are known to have a high incidence of duodenal ulcer, but increasing urbanization and the stress of city life may also play a part, as suggested by Segal et al. and Levin et al. in black South Africans.

The pattern of ulceration is similar to that seen in southern Nigeria with pyloric stenosis the commonest complication. Not a single case of gastric ulcer was recorded in this series, confirming the finding that gastric ulcer is uncommon throughout Africa.

Interestingly there are distinct differences between this series and those reported from Zaria, also in the northern savannah, where gastric ulcer is relatively common and perforation is the commonest complication; it has been suggested that this might be a distinctive feature of the savannah, a finding not confirmed by this study.

Since the introduction of H2 blockers the number of patients undergoing ulcer surgery for 'failed medical management' has been declining. In this series 11 of 44 (25%) patients presenting with uncomplicated ulcer were treated by surgery, nine by truncal vagotomy and drainage. It may well be that this high rate of operation is appropriate in the special circumstances of the developing world.

Duodenal ulcer is a chronic relapsing condition, 80% of patients will relapse within one year after healing with an H2 blocker, while Marks et al. reported a recurrence rate of 46% even on maintenance with H2 blockers in South Africa. Most patients cannot afford repeat courses of H2 blockers and many live far away from the hospital so that if their recurrent ulcer is heralded by perforation or a major upper gastrointestinal bleed they are very likely to die before reaching hospital.

Long term cure of the ulcer is therefore particularly important. Eradication of Helicobacter pylori has for the first time offered the possibility for a 'medical cure' for duodenal ulcer, with relapse rates of 21% at one year in those in whom H. pylori is eradicated compared with 83% in patients in whom H. pylori persists. However this is untried in Africa where the prevalence of infection is much higher and re-infection rates unknown.

An alternative for the endoscopically or barium meal proven recurrent ulcer is a truncal vagotomy and drainage; a relatively simple operation with a low mortality and 7% five year recurrence rate.
ACKNOWLEDGMENTS

We would like to thank the staff of the medical records department at the University of Maiduguri Teaching Hospital for their help and cooperation.

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HELICOBACTER PYLORI: THE AFRICAN ENIGMA

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Data on Helicobacter pylori (H. pylori) infection in Africa is at odds in several aspects with that published from the West. Gastric H. pylori infection is common, almost ubiquitous in Africa; but the pattern of infection, age of acquisition, environmental, dietary and genetic influences are different from those in the West. These differences alter the pathological role and clinical relevance of the organism in Africa where, apart from gastritis, there is no established correlation between H. pylori infection and upper gastrointestinal disease.

**Epidemiology**

The measurement of circulating antibodies to H. pylori using an enzyme linked immunosorbant assay provides a simple, reliable and non-invasive means of diagnosing H. pylori infection, with a sensitivity of 95% and specificity of 85% (1). This technique is adaptable, can be used in large numbers of subjects and has been used to map the epidemiology of H. pylori infection worldwide (2,3). Random serological studies have demonstrated that most of the population in Africa are infected by H. pylori for most of their lives, with 70-80% of the population having antibodies to H. pylori (4,5). Not only is infection common but it is acquired at an early age. Fifty five percent of the population under age ten have IgG antibodies to H. pylori in the Ivory Coast (4), while half of children aged under five have IgG antibodies to H. pylori in northern Nigeria (6) and the Gambia (7). These figures derived from serological studies have been confirmed by culture and histological examination of gastric mucosal biopsies. Seventy to ninety seven percent of patients with dyspepsia are infected by H. pylori (8-13), as are 80% of asymptomatic volunteers (12,14).

With such a high prevalence of infection a high prevalence of those diseases said to be associated with H. pylori infection would be expected.
Gastritis

Gastritis is very common throughout Africa and shows a strong correlation with H. pylori infection. Indeed, as in the West, type B antral gastritis is a good indicator of H. pylori infection. In endoscopic studies histological gastritis is present in 80-100% of subjects with dyspepsia (8-13) and was found in 88% of a group of 40 asymptomatic controls (14).

Duodenal Ulceration

The prevalence of duodenal ulcer shows marked variation in different parts of Africa; a subject comprehensively reviewed by Tovey and Tunstall (15) who defined areas of high incidence (Nile/Congo watershed and coastal region of West Africa) and low incidence (northern savannah of West Africa). These differences in incidence are not paralleled by differences in the prevalence of H. pylori infection.

In the dry savannah of northern Nigeria duodenal ulcer is uncommon. This was first noted by Tovey and Tunstall (15) and recently confirmed (16). In a random community survey 28% of adults had experienced dyspepsia in the preceding six months (16), a figure remarkably similar to the 25-38% recorded in the UK (17-19). Using the same definition of dyspepsia, and in the same population duodenal ulcer was found in only 18 of 162 patients, who were endoscoped for their dyspepsia (20); a prevalence of 111/1000 patients with dyspepsia, compared to 178-305/1000 in the UK (17-19). Duodenal ulceration is then less common in northern Nigeria than in the UK despite the higher prevalence of H. pylori infection.
Gastric ulcer is a rare disease in Africa, occurring 6 to 30 times less commonly than duodenal ulcer (21-25). In northern Nigeria duodenal ulcer is uncommon, yet gastric ulcer is six times less common (8). In Ethiopia Tsega found only 5 gastric ulcers in 1084 gastroscopies, compared to 154 duodenal ulcers (26). Yet gastritis, which is believed to be fundamental to the cause of gastric ulcer (27), is present in 90% of Africans and H.pylori which is associated with gastric ulcer in the West is present in over 80% of Africans (8-13).

Gastric Cancer

H.pylori causes gastritis and as such it is suggested as a precursor of gastric cancer (28). Forman, et al have documented an increased incidence of gastric cancer with increased prevalence of H.pylori infection in China (29) and in a case control study in Wales an odds ratio of 2.8 has been calculated for the risk of gastric cancer in those infected by H.pylori (30), similar figures have also been recorded in the USA (31).

In Nigeria H.pylori gastritis is common yet gastric cancer is uncommon. In the absence of accurate population statistics the most useful indicator of tumour incidence is the proportional frequency of one tumour compared to that of all other tumours (32). Using this measure gastric cancer accounts for less than 2% of all malignant tumours in northern Nigeria (33,34) and only 2-3% of malignancies in the Sudan, Uganda and Zimbabwe (35-37).

Why when H.pylori gastritis is common are these associated diseases uncommon?
Dixon suggest that H. pylori leads to ulceration only in gastric metaplasia in the duodenum (38) and this is increased in hyperacidity (39). Studies from Africa have shown lower basal and maximal acid outputs in asymptomatic controls (40-42) compared to the UK (43,44). It is reasonable to suggest that there is less acid, less gastric metaplasia, less duodenal H. pylori infection and therefore less duodenal ulcer. There is certainly a need to document the prevalence of duodenal gastric metaplasia in Africa and to correlate this with the prevalence of duodenal ulcer. If there is a good correlation this would support the suggestion that it is a combination of gastric metaplasia in the duodenum and H. pylori infection which is fundamental to the pathological role of H. pylori in duodenal ulcer. But why do Africans, infected by H. pylori, produce less gastric acid when western subjects with H. pylori infection have been shown to have increased levels of gastric acid (45)?

A low prevalence of gastric metaplasia does not account for the low prevalence of gastric ulcer (21-25), which requires neither high acid output or gastric metaplasia in the duodenum. Graham has suggested that H. pylori infection acquired at a young age is less pathogenic than that acquired as an adult, a situation analogous to paralytic poliomyelitis which is more likely to occur if infection is acquired after infancy (46). With most infection in Africa acquired in early childhood (6,7) this may be important.

Different strains of H. pylori may have different pathogenicity. It has been suggested that organisms showing a gastric IgA response to the 120 kDa protein are more likely cause peptic ulcers (47). It would be of interest to map the strain types in Africa and to correlate this with the incidence of peptic ulcer. This will become practical if a systemic marker of the H. pylori pathogenicity is identified.
affects of H. pylori. Of these, diet may play an important protective role. In India, areas of high and low incidence for duodenal ulcer have been identified and clearly correlated with diet (48). A pulse, lentil, okra and millet diet is protective, while a refined rice diet is not (49). The staple diet in northern Nigeria is of millet with large amounts of okra (personal observation) which may well, as in India, help to prevent duodenal ulcer. Other environmental and social factors are also different, for instance, few subjects smoke or take non-steroidal anti-inflammatory drugs in northern Nigeria (16).

Gastric cancer is a tumour of old age. The life expectancy in Nigeria is only 55 and in the West gastric cancer is uncommon below this age. However, if an H. pylori induced gastritis is an important initial step in some, it is the age at which the gastritis first occurs which may be important. H. pylori infection and gastritis occurs 20-30 years earlier in Africa compared to the West (6,7), but this has not led to an increase in gastric cancer in early middle age. The peak incidence for gastric cancer in South Africa is in the seventh decade (50).

The incidence of gastric cancer is thought to be higher in stomachs with intestinal metaplasia (51,52) and it has been suggested that intestinal metaplasia is the result of long term gastric inflammation possibly secondary to H. pylori infection (53). Of interest then is the low prevalence of intestinal metaplasia in Africa. In H. pylori positive patients in the West, 17 to 30% have intestinal metaplasia present in gastric biopsies (28,54). In a series of 157 patients with non-ulcer dyspepsia and 40 asymptomatic controls in Nigeria, intestinal metaplasia was present in only 2% (personal observation) an observation noted in reports from other African countries (11,55). It is likely that environmental and/or genetic factors which cause the change from gastritis to intestinal metaplasia and subsequently dysplasia and cancer are not present.
Geographical variations in the incidence of peptic ulceration and gastric cancer have been apparent for many years, but in Africa these are not accounted for by variations in the prevalence of H. pylori infection. Indeed, with the exception of gastritis, the case for a pathological role for H. pylori in Africa is unproven.

Above all else the data from Africa underlines the multifactorial nature of the cause of peptic ulcer and gastric cancer. H. pylori exerts its influence in concert with other environmental, social and genetic factors. The relative importance of these and how they interact in a given community or individual remains to be elucidated.
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Helicobacter pylori clearance in the treatment of non-ulcer dyspepsia

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Accepted for publication 6 August 1991

SUMMARY

One hundred and thirty north Nigerian patients with non-ulcer dyspepsia were treated with amoxycillin and chelated bismuth, or antacid. Symptoms resolved in 28 (33%) of bismuth and amoxycillin recipients completing the trial compared with 1 (4%) of antacid recipients. Response did not relate to Helicobacter pylori clearance.

INTRODUCTION

The role of gastric Helicobacter pylori (H. pylori) infection in the aetiology of non-ulcer dyspepsia is unclear. A higher prevalence of H. pylori infection has been reported in those with non-ulcer dyspepsia than controls,1 but the therapeutic response to the clearance of H. pylori has been disappointing.2 In Africa H. pylori infection has been reported in 70-80% of patients with dyspepsia;3,4 however antibodies to H. pylori have also been found in 70-85% of the normal population5 and the pathological significance of H. pylori infection in this environment is unknown. Non-ulcer dyspepsia is common in northern Nigeria and a cause of considerable morbidity,6 we have therefore compared responses to treatment of
symptoms of H. pylori clearance.

MATERIALS AND METHODS

Definition of non-ulcer dyspepsia and trial entry criteria
Non-ulcer dyspepsia was defined according to the criteria of the Management of Dyspepsia Working party.7 Patients were recruited for the study if they fulfilled the following strict entry and exclusion criteria: chronic epigastric pain of at least three months duration plus two of the following: exacerbation or relief by meals, exacerbation by hunger, night waking, heartburn, relief of pain by antacids or milk, and epigastric tenderness. Patients were excluded if they had taken antibiotics, bismuth containing compounds, or anti-ulcer drugs other than simple antacids in the previous month or had other pathology which may have accounted for the dyspepsia, e.g. peptic ulcer, irritable bowel syndrome (diagnosed according to the criteria of Manning et al.;8 gall bladder disease or tropical pancreatitis.

Diagnosis
Patients had a standard proforma completed, and then underwent upper gastrointestinal endoscopy at which peptic ulceration was excluded. Two biopsies were then taken from the gastric antrum and one from the gastric body, one from the antrum for culture and the other two for histological examination. Histological specimens were stained with hamatoxylin and eosin and examined for the presence of H. pylori and gastritis. Antral cultures were set up where possible within 3 h of biopsy depending upon microbiologist availability.

Study organisation
The standard treatment for dyspepsia in this environment is antacid; this was compared with an anti-H. pylori treatment. Those given the anti-H. pylori treatment were further analysed to determine the effect of H. pylori clearance on symptoms. Patients were randomized on a 1 to 3 basis to either Gelusil (500 mg magnesium trisilicate and 250 mg of aluminium hydroxide, Warner Lambert) one tablet four times daily, or to tripotassium dicitratobismuthate (De Nol Tabs, Gist Brocades) 240 mg four times daily for 28 days together with amoxycillin 500 mg four times daily for the first 14 days. Compliance was assessed at follow up by asking each patient how many, if any, tablets remained.

Criteria of response and follow-up
Non-ulcer dyspepsia is a subjective sensation. To make assessment as objective as possible, complete resolution of symptoms at one month of follow-up was chosen as the principle criterion of response, the patients being followed up at one month (at the end of treatment) by clinical assessment, repeat endoscopy and biopsy.
The \( \chi^2 \) test was used with Yates correction or Student's \( t \) test where necessary, for comparison of the baseline data and the difference in symptom resolution. Confidence limits were calculated for the difference in percentages.

RESULTS

One hundred and thirty patients fulfilled the study entry criteria and were randomised to bismuth and amoxycillin (\( n = 98 \)) or antacid (\( n = 32 \)). One hundred and nine patients were available for follow-up; bismuth and amoxycillin \( n = 86 \) (88\%), antacid \( n = 23 \) (72\%).

Of the 23 patients who had received antacid symptoms resolved in only 1 (4\%; 95\% confidence limits —4 to 13\%), compared to 28 of 86 of those who had taken bismuth and amoxycillin (33\%; 95\% confidence limits 23–43\%), a significant difference (\( P < 0.01 \)).

Of the 86 patients who had received bismuth and amoxycillin and were available for follow up; 61 were infected with \( H. pylori \) at entry to the trial. Of these 61 patients \( H. pylori \) was cleared in 29 (48\%) and remained present on histological examination of antral biopsies in 32. There was no difference between these two groups on baseline assessment (see Table 1).

There was no significant difference in therapeutic response between these two groups; symptoms resolved in 11 of 29 patients (38\%; 95\% confidence limits 20–56\%) in whom \( H. pylori \) was cleared and in 9 of 32 (28\%; 95\% confidence limits 12–44\%) in those in whom \( H. pylori \) was not cleared.

DISCUSSION

Bismuth and amoxycillin was significantly better at achieving symptom resolution than antacid. However this was not due to its anti-\( H. pylori \) action.

Bismuth has a well-documented cytoprotective action, while amoxycillin is active against a number of different intercurrent infections which may be present, undiagnosed in this developing world population. Both these actions and the possible placebo effect of bismuth and amoxycillin, which may be greater than that achieved by antacid, may account for the increased efficacy over and above antacid.

This study falls short of the ideal and typifies both the problems experienced in trials of \( H. pylori \) clearance in non-ulcer dyspepsia and the problems encountered in the developing world, where patient follow up and tracing of defaulters is difficult. Follow up was further compromised by damage to the gastroscope, which had to be sent to the UK for repair.

The trials of anti-\( H. pylori \) treatment reported in the literature give conflicting results. Only the trials of McNulty et al.\(^9\) and Lambert et al.\(^\) show improvement in symptoms related to \( H. pylori \) clearance, and that reported by McNulty does not
reach statistical significance. Rokkas et al.\textsuperscript{11} did not relate symptom improvement to clearance of the organism, Borady et al.\textsuperscript{12} did not find any relation between symptoms and bacterial clearance while, Loffeld et al.\textsuperscript{2} did not find any improvement in symptoms in those taking bismuth over and above placebo. All the trials have been in relatively small numbers of patients.

It is difficult to apply these figures from Africa to the West. The pattern of infection, environmental factors and social habits are all markedly different. In Africa \textit{H. pylori} infection is acquired in early childhood,\textsuperscript{13} with 80\% of the population infected before 10 years of age, compared to only 3\% in the UK.\textsuperscript{14} It may be that the early age at which infection is acquired causes a different host response\textsuperscript{15} and is less likely to cause dyspepsia.

While there is little support from this study for an aetiological role for \textit{H. pylori}, the apparent benefit of bismuth and/or amoxycillin demonstrated in this study deserves further investigation in a randomized, double-blind trial.

\textbf{ACKNOWLEDGEMENTS}

This study was funded by a grant from the Stanley Thomas Johnson Foundation.


**H. pylori, the Most Common Bacterial Infection in Nigeria: A Random Serological Study**

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This study was carried out to determine the prevalence of antibodies to *Helicobacter pylori* in northern Nigeria, a region with a low incidence of peptic ulceration. In a random, serological survey of 268 subjects, 228 (85%) of the population studied had IgG antibodies to *H. pylori*. Fifty-eight of these subjects had experienced dyspepsia in the preceding 6 months. The majority of the population (82%) is infected between the ages of 5 and 10. Despite the high prevalence of antibodies to *H. pylori*, peptic ulcer is uncommon, suggesting that *H. pylori* is not important in the etiology of peptic ulcer in this population. Indeed, most patients infected by *H. pylori* are asymptomatic. The possible reasons for this are discussed.

**INTRODUCTION**

*Helicobacter pylori* causes type B antral gastritis (1), and it has been suggested that it is important in the etiology of peptic ulceration (2). Vital to any discussion of the pathological role of *H. pylori* is a consideration of its prevalence in the general population. The prevalence of infection varies with age (3) and ethnic group (4), and valid comparisons can be made only between groups that are matched for these factors. The prevalence of *H. pylori* infection in normal populations is poorly documented, particularly in the "developing world." This study is a serological survey of IgG antibodies to *H. pylori* in a randomly chosen rural population in northern Nigeria.

**METHODS**

The survey was conducted in five villages in northern Nigeria close to the state capital Maiduguri. This area is dry savannah just south of the true desert. The population is predominantly Muslim, and most are rural subsistence farmers.

Houses in each village had been previously numbered as part of the government's primary health care program, and households to be surveyed were chosen by means of a table of random numbers. Within each household, all occupants over the age of 5 yr were interviewed by medical students and requested to give a 5-ml blood sample. Not all subjects were prepared to give blood, in which case the interviewers moved onto the next randomly chosen household. Details were recorded of previous dyspepsia, defined as epigastric pain related to males and/or exacerbated by hunger. Subjects were also questioned about night waking, relief by milk or antacids, and were examined for epigastric tenderness.

Serum was tested at the Public Health Laboratory, in Manchester, UK. The serum was dried on filter paper and sent by courier and post; this was eluted on arrival in the laboratory. The serum was tested by standard enzyme-linked immunosorbant assay (ELISA) technique (5) to detect IgG antibodies to whole cell *H. pylori* antigens, a technique previously validated in the UK (3).

Some of the surface antigens for *H. pylori*, in particular, the flagella proteins, have epitopes in common with *Campylobacter jejuni* (6), and therefore, all sera were absorbed with *C. jejuni* before testing for *H. pylori* antibodies.

In any ELISA, the absorbance cut-off level for validated negatives must be determined. This is particularly true of the present study, in which—due to the handling of the serum—the resulting absorbance levels may not be exactly the same as might be obtained with serum from the UK.

The ELISA absorbance levels were measured on the serum of 30 patients known to be infected by *H. pylori* from the results of culture and histological examination of endoscopic biopsies. These were patients presenting to the University of Maiduguri Teaching Hospital with dyspepsia. Each patient was gastroscoped, and two mucosal biopsies were taken from the gastric antrum and one from the gastric body. One specimen was cultured in a microaerophilic environment produced by means of a gas-generating kit (Oxoid, BR60) and two were fixed in formalin, stained with hematoxylin and eosin, and examined for gastritis and the presence of *H. pylori*. The absorbances were all above 0.500, with a mean of 0.900. In a search for uninfected subjects, two further groups were studied: Nigerian infants aged 6 months to 2 yr (n = 21) and British expatriates living in Nigeria (n = 11). These subjects were not gastroscoped; however, the absorbances were clearly divided into two groups, below 0.4 (uninfected) and above 0.6 (infected), with a small number of subjects in between (4 of 32). On the basis of this, the negative absorbance reading for this assay was established at < 0.5.

The validity of this level was confirmed by comparing the prevalence of *H. pylori* antibody found in the serological survey with the prevalence of antibody in an age-matched group of 40 asymptomatic volunteers, mainly medical students and hospital staff from the University of Maiduguri Teaching Hospital, who were gastroscoped and had their infection confirmed by culture and histological examination. The mean age of this asymptomatic group was 23 yr, of whom 80% were infected by *H. pylori*, compared with an antibody prevalence of 79% in the community (age 20–29).

This study was approved by the Research and Ethics Committee of the College of Medical Sciences of the University of Maiduguri.
Serum was collected from 268 subjects over the age of 5 yr. The mean age of the sample was 35 yr, of whom 228 (85%) had antibodies to H. pylori, and 40 (15%) were negative (see Table 1). All of the subjects were from northern Nigeria, mostly from the Kanuri ethnic group (81%). There was no significant increase in the prevalence of infection with increasing age in the population studied, suggesting that most subjects are infected before the age of 5 yr. In a small group of children, aged 6 months to 2 yr, 57% (12 of 21) had antibodies to H. pylori.

Of the 268 randomly chosen subjects, 58 had experienced dyspepsia in the preceding 6 months. The mean age of this group was also 35 yr (47), 81% had antibodies to H. pylori, and 11 (19%) were negative.

**DISCUSSION**

The level of antibodies to H. pylori infection (85%) in this community is the highest that has been reported. Particularly notable is the early age at which it was acquired. Fifty-seven percent of a small group of children aged 6 months to 2 yr have antibodies, as do more than 80% of 5- to 9-yr-old children.

These findings confirm other reports from Africa. Megraud et al. (4) found antibodies in 265/374 (71%) of randomly chosen subjects in the Ivory Coast, and in 218/277 (79%) subjects in Algeria, whereas Glupzyenski et al. found antibodies in 104 of 132 (79%) subjects in Zaire (7). The study of Megraud et al. (4) also confirms the young age of initial infection: 64 of 116 (55%) subjects under the age of 9 yr had antibodies to H. pylori in the Ivory Coast and 19 of 42 (45%) in Algeria.

This very high level of infection, which occurs throughout Africa (see above), makes H. pylori infection one of the commonest bacterial infections in Africa, and is in stark contrast to the prevalence of infection in Western populations, where very few children are infected, and the prevalence rises with age to only 50% at 60 yr of age (3, 8).

Most people with H. pylori infection in Africa are asymptomatic; only 38 of 268 subjects in this study had experienced dyspepsia in the preceding 6 months, and there was no significant differences between the prevalence of infection in this group and the general population.

Despite the high prevalence of antibodies to H. pylori, the available data suggest that there is a low incidence of peptic ulcer in the northern savannah of Nigeria, as noted by Tovey and Tunstall (9). The true prevalence of peptic ulceration is difficult to measure, and this is particularly so in Africa with, inadequate population statistics and access to health care. However, in a recent survey of the prevalence of dyspepsia in northern Nigeria, the prevalence rate of peptic ulceration was estimated at 32/1000 (10), less than half that found in the UK (11) and only a third of that found in Norway (12). This apparent contradiction emphasizes the fact that H. pylori is only one of a number of factors predisposing to peptic ulceration.

**H. pylori infection does not necessarily run a uniform course. Yoshimura et al. (14) have recently suggested that the strain of H. pylori associated with peptic ulceration differs at the genomic level from that which causes asymptomatic gastritis; it may be that the most common strain of H. pylori in Nigeria causes only a benign infection. Alternatively, there may be a different host response to H. pylori determined by the age at which infection is acquired (15), with infection running a more benign course if acquired in childhood, as is the case in Nigeria.**

H. pylori causes gastritis (1), is commonly associated with intestinal metaplasia, and has been suggested as a possible etiological factor for gastric cancer (16). However, gastric cancer is an uncommon tumor in northern Nigeria, accounting for only 2–3% of all malignant tumours seen (17, 18).

**Conclusion**

H. pylori infection is very common in Africa and, apart from causing histological gastritis, seems to cause no untoward effects.

**ACKNOWLEDGMENT**

We would like to thank the medical students of the College of Medical Sciences, University of Maiduguri, Nigeria, for their help with this study.

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