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Clinical trial with inactivated hepatitis A vaccine and recommendations for its use

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Abstract

***Objective*—To compare the reactogenicity and immunogenicity of an inactivated hepatitis A vaccine in two different immunisation schedules.**

***Design*—Randomised trial.**

***Setting*—One London teaching hospital.**

***Subjects*—104 healthy adult volunteers (71 men, 33 women aged 19-60).**

***Interventions*—Hepatitis A vaccine to group 1 (54 volunteers) at 0, 1, and 2 months and to group 2 (50) at 0, 1, and 6 months.**

***Main outcome measures*—Symptoms at and after each dose; liver function, hepatitis A virus specific serum immune response; and responses in saliva and parotid fluid in immunised volunteers and subjects with natural immunity.**

***Results*—The vaccine was well tolerated; 97% (96/99) and 100% of those immunised developed serum antibody after one and two doses of vaccine respectively. Geometric mean titres increased progressively after each dose and were significantly higher in men but not women in group 2 after the third dose (ratio between geometric mean titres 0·265, 95% confidence interval 0·18 to 0·39; $p<0·0001$). At one year this group-sex interaction was absent; geometric mean titres for both sexes were significantly higher in group 2 (ratio 0·330, 0·227 to 0·478; $p<0·0001$). Antibody responses were not significantly different between the groups at two years. Compared with naturally infected subjects immunised volunteers developed poor or undetectable virus specific IgG and IgA responses in saliva and parotid fluid.**

***Conclusions*—The vaccine was safe and highly immunogenic, and the differences in the immune responses in saliva and parotid fluid are unlikely to affect its efficacy.**

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Introduction

The first hepatitis A vaccine, comprising formalin inactivated virus extracted from marmoset liver, was shown to be both immunogenic and protective in marmosets as long ago as 1978.[1] It was not until the following year, however, that hepatitis A virus was propagated in tissue culture,[2] making large scale vaccine production feasible. Owing to poor yield of virus in cell culture and because until recently priority has been given to other vaccines, particularly hepatitis B vaccine, it is only now, more than a decade later, that a hepatitis A vaccine is available in the United Kingdom.

Although hepatitis A virus does not lead to chronic liver disease and is frequently subclinical in young subjects, infection can be severe, with fulminant hepatic failure, particularly in older persons. In the United Kingdom, for example, hepatitis A is responsible for about a fifth of cases of fulminant viral hepatitis,[3] and a mortality of 1·5% in subjects aged over 64 has been recorded.[4] Furthermore, a prolonged or relapsing course is recognised,[5,6] and it has recently been suggested that hepatitis A virus may act as a trigger for autoimmune chronic active hepatitis in susceptible subjects.[7]

Over the past few years considerable effort has been directed towards developing live attenuated[8,9] and inactivated[10] hepatitis A vaccines. An inactivated hepatitis A vaccine has just become available, and we describe a trial of a formalin inactivated whole virus hepatitis A vaccine in adult volunteers, comparing immunogenicity in two different schedules. In addition, we compare salivary and parotid antibodies in immunised volunteers and people with natural immunity and discuss the potential use of this vaccine both in the United Kingdom and in developing countries.

Subjects and methods

HEPATITIS A VACCINE

The vaccine was prepared from the HM175 strain (RIT 4380) grown on MRC-5 cells. Virus was purified by ultrafiltration and gel chromatography, inactivated with formaldehyde, and adsorbed on to aluminium hydroxide.[11]

Each 1 ml dose of vaccine contained 720 ELISA (enzyme linked immunosorbent assay) units of killed hepatitis A virus, measured by means of a capture ELISA.[11]

VOLUNTEERS

One hundred and five healthy adult volunteers (medical students, doctors, and laboratory staff) gave written informed consent to participate in the trial, which had local ethical approval. Analyses of reactogenicity and immunogenicity were carried out on 104; one volunteer was excluded owing to an irregular immunisation schedule. Table I summarises the demographic details of the volunteers. All volunteers were negative for hepatitis A virus specific IgG and they were aged between 19 and 60 years (mean and median ages 30·8 and 29 respectively); 71 were men and 33 were women.

TRIAL PROTOCOL

We stratified the volunteers according to age (>30 and <30) and sex into four groups. Within each group the subjects were allocated randomly into one of two vaccine schedules: group 1 to receive vaccine at 0, one, and two months and group 2 at 0, one, and six months. The dose schedules selected were those in current use

TABLE I—*Demographic details of 104 volunteers included in analyses of reactogenicity and immunogenicity of inactivated hepatitis A vaccine*

Sex	No	Age (years) Minimum	Maximum	Median	Mean	SD
			Group 1			
Male	36	20	56	29	31·3	9·53
Female	18	21	47	29	31·7	9·46
Total	54	20	56	29	31·4	9·42
			Group 2			
Male	35	20	60	28	29·8	9·32
Female	15	19	47	30	30·9	8·17
Total	50	19	60	29	30·1	8·93
			Groups 1 and 2			
Male	71	20	60	29	30·6	9·40
Female	33	19	47	30	31·3	8·77
Total	104	19	60	29	30·8	9·17

for hepatitis B vaccine, as a combined vaccine against hepatitis A and B viruses may be introduced in due course. Vaccine was given into the deltoid muscle.

Blood samples were taken before entry to the trial; at one, two, three, six, seven, and 12 months during the trial; and from 53 of the volunteers at 24 months. Liver enzymes were monitored with standard laboratory techniques.

Side effects and body temperature were recorded on a questionnaire on the day of immunisation and for three days after each dose. Symptoms were divided into local, general, or "other" and were graded according to severity.

Saliva samples were collected with salivettes (Sarstedt, Leicester) from 19 volunteers (nine from group 1, 10 from group 2) at weekly intervals until month 3 and between months 6 and 7. For comparison samples were collected from 11 adults with naturally acquired serum hepatitis A specific IgG, none of whom gave a history of jaundice. Samples were also taken from 10 volunteers (four from group 1, six from group 2) about two years after the first dose and from four people with naturally acquired immunity in order to compare serum, salivary, and parotid antibody responses; parotid fluid was collected with a Lashley cup (fig 1).

SEROLOGICAL TESTING

A competitive ELISA (HAVAB EIA, Abbott Laboratories, North Chicago, Illinois) was used to screen for hepatitis A virus antibody in blood samples taken before entry to the trial. After immunisation hepatitis A vaccine antibody titres were measured with an ELISA inhibition assay. Titres were calculated in mIU/ml by comparison with a standardised immunoglobulin preparation obtained from the World Health Organisation, using the four parameter method.[12] Serum samples containing <20 mIU/ml antibody were deemed negative. Samples of saliva and parotid fluid were tested for hepatitis A virus specific IgM, IgA, and IgG by antibody capture radioimmunoassay.[13]

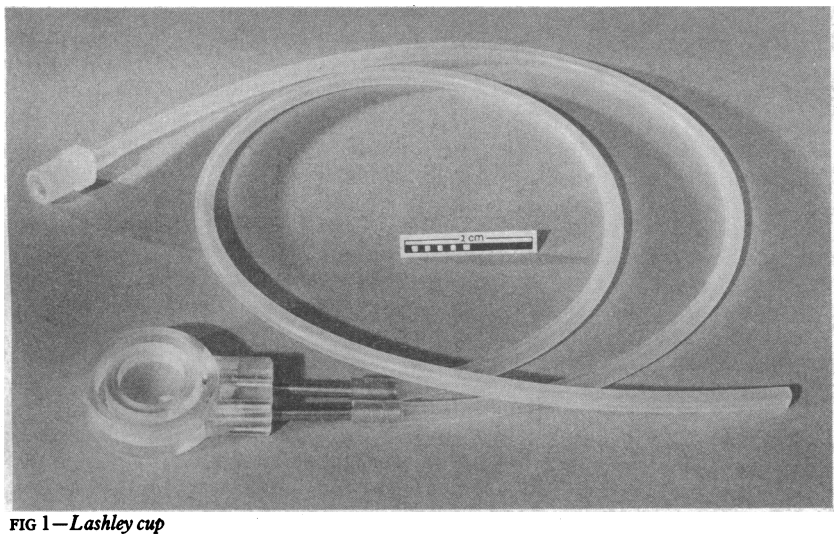

FIG 1—*Lashley cup*

STATISTICAL ANALYSIS

Serological responses between groups 1 and 2 and men and women were compared by the unpaired Student's *t* test, with logarithmically transformed data. Analysis of variance was used to determine the extent of any group-sex interaction.

Results

SAFETY AND REACTOGENICITY

A total of 311 doses of vaccine were given, and 308 symptom sheets were analysed (table II). In all, 148 (48%) doses elicited no side effects. Table III shows the incidence of local and general symptoms. At least one local symptom was recorded after 44% of injections and the most common symptom, recorded after 124 doses (40%) was mild soreness at the injection site lasting from one to two days. General symptoms were less common, occurring after only 73 doses (24%); those recorded most frequently were fatigue (10%) and headache (7%). The incidence of adverse reactions decreased with successive doses of vaccine.

There was no evidence of vaccine induced hepatocellular damage. A few mild, asymptomatic, and transient increases in liver transaminases occurred, which did not generally correlate with administration of vaccine; none were considered to be vaccine related.

IMMUNOGENICITY

A single dose of vaccine induced an immune response in 97% (96/99) of those immunised, seroconversion rates being similar in the two groups (table IV). The

TABLE II—*Volunteers with and without symptoms after each dose of hepatitis A vaccine*

Dose No	Group	No of symptom sheets	No (%) with symptoms	No (%) without symptoms
1	1	54	35 (65)	19 (35)
	2	50	39 (78)	11 (22)
2	1	52	27 (52)	25 (48)
	2	50	25	25
3	1	52	13 (25)	39 (75)
	2	50	21 (42)	29 (58)
Total	1	158	75 (48)	83 (53)
	2	150	85 (57)	65 (43)
Total	1 and 2	308	160 (52)	148 (48)

TABLE III—*Incidence of local and general symptoms reported*

Dose No	Group	No of symptom sheets	No (%) symptoms reported: Local alone	General alone	Local and general	Local*	General†
1	1	54	18 (33)	4 (7)	13 (24)	32 (58)	18 (33)
	2	50	22 (44)	6 (12)	11 (22)	33 (66)	17 (34)
2	1	52	19 (37)	4 (8)	4 (8)	24 (46)	8 (15)
	2	50	15 (30)	3 (6)	7 (14)	22 (44)	10 (20)
3	1	52	6 (12)	4 (8)	3 (6)	10 (19)	7 (13)
	2	50	8 (16)	6 (12)	7 (14)	15 (30)	13 (26)
Total	1	158	43 (27)	12 (8)	20 (13)	66 (42)	33 (21)
	2	150	45 (30)	15 (10)	25 (17)	70 (47)	40 (27)
Total	1 and 2	308	88 (29)	27 (9)	45 (15)	136 (44)	73 (24)

*Subjects with at least one local symptom.
†Subjects with at least one general symptom.

TABLE IV—*Seroconversion rates and geometric mean titres of antibody after administration of hepatitis A vaccine*

Timing of doses (months)	Men				Women			
	Seroconversion rate	Geometric mean titre	95% Confidence interval	Range	Seroconversion rate	Geometric mean titre	95% Confidence interval	Range
				Group 1				
1	32/33	166	114 to 229	20-1162	17/17	268	181 to 397	82-915
2	35/35	257	197 to 337	65-1394	17/17	479	329 to 697	120-1640
3	35/35	666	513 to 867	214-3681	15/15	1924	1265 to 2924	544-5598
6	33/33	540	418 to 697	62-2327	16/16	1167	824 to 1652	284-3806
7	34/34	460	368 to 573	77-1830	14/14	813	505 to 1309	133-2777
12	35/35	342	302 to 437	74-1202	16/16	728	427 to 1219	47-2547
24	20/20	252	162 to 394	45-1384	9/9	798	360 to 1770	82-2093
				Group 2				
1	32/34	199	139 to 285	20-869	15/15	400	252 to 635	72-981
2	35/35	257	188 to 349	25-3230	15/15	361	277 to 472	190-1028
3	34/35	227	160 to 321	33-1273	14/14	402	310 to 520	138-894
6	32/34	202	138 to 296	35-1024	15/15	425	301 to 598	160-1216
7	34/34	2520	1871 to 3388	206-13560	15/15	2752	1923 to 3946	948-10452
12	34/34	1174	828 to 1667	143-9990	15/15	1698	995 to 2897	254-8279
24	13/13	364	196 to 675	53-1274	11/11	1057	594 to 1879	164-2678

TABLE V—*Hepatitis A virus specific antibody in saliva in subjects with naturally acquired and vaccine induced immunity*

	Immunoglobulin		
	IgM	IgA	IgG
Naturally acquired immunity (n=11)	0	5	11
Vaccine induced immunity (n=19)	4*	0	2†

*Transient responses during first month after first dose.
†Both in group 2, becoming positive after the third dose.

TABLE VI—*Hepatitis A virus specific immune responses in saliva and serum in 10 immunised volunteers at 24 months*

Volunteer No	Salivary IgG (test/negative ratio)	Serum IgG (mIU/ml)
1	9·2	2454
2	8·5	1273
3	4·9	1541
4	3·8	1033
5	3·3	1125
6	3·2	1248
7	2·5	261
8	1·6	312
9	1·3	779
10	1·2	501

three subjects who did not seroconvert after this initial dose were men aged over 40. One hundred per cent seroconversion was achieved after the second dose, and in both groups geometric mean titres rose progressively with each dose of vaccine. One month after the final dose there was no significant difference in geometric mean titres between the two schedules among women, but men in group 2 had a significantly higher response than those in group 1 (ratio between geometric mean titres 0·265, 95% confidence interval 0·18 to 0·39; $p<0·0001$) (fig 2). At one year this group-sex interaction was absent, geometric mean titres for both sexes being significantly higher in group 2 (ratio between geometric mean titres 0·330, 0·227 to 0·478; $p<0·0001$). When antibody responses between the two groups were compared at two years there was no significant difference.

Table V summarises the salivary antibody responses

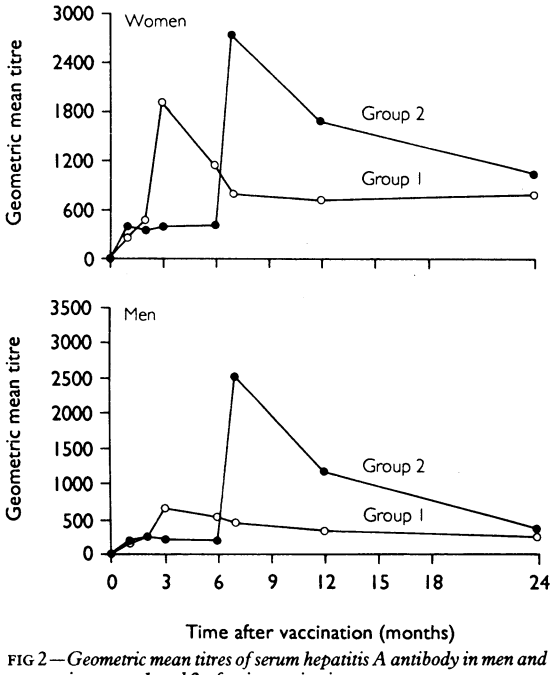

FIG 2—*Geometric mean titres of serum hepatitis A antibody in men and women in groups 1 and 2 after immunisation*

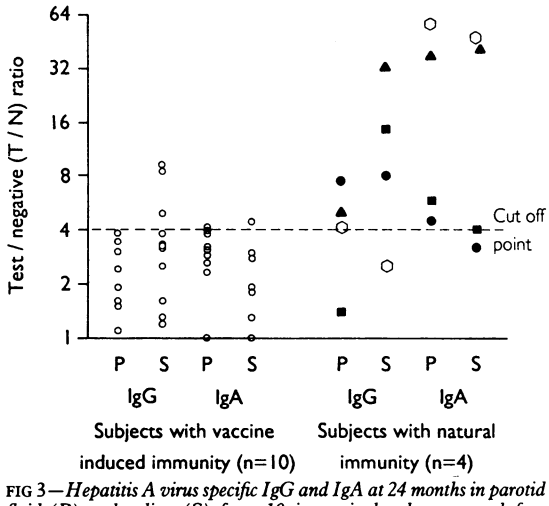

FIG 3—*Hepatitis A virus specific IgG and IgA at 24 months in parotid fluid (P) and saliva (S) from 10 immunised volunteers and four subjects with naturally acquired immunity (●, ■, ▲, ○). Positive results have a test/negative ratio >4*

in the 19 immunised volunteers and 11 subjects with naturally acquired immunity. Hepatitis A virus specific IgG was detected in all of those with natural immunity and virus specific IgA in nearly half. Among immunised volunteers, however, hepatitis A virus specific IgA was absent, and virus specific IgG was detected in only two (11%), both of whom had relatively high serum antibody titres (4968 and 2633 mIU/ml respectively). In four (21%) volunteers a low titre of hepatitis A virus specific IgM was detected transiently in the month after the first dose of vaccine.

Figure 3 compares the hepatitis A virus specific immune responses at 24 months in saliva and parotid fluid in subjects with vaccine induced and naturally acquired immunity. The levels of virus specific IgG and IgA in the naturally infected subjects were mainly above the cut off point, often at high levels. Levels of IgG in parotid fluid and saliva correlated but IgA responses did not. The levels of hepatitis A virus specific IgG and IgA in parotid fluid and saliva from most immunised volunteers, however, fell below the cut off point; the three volunteers in whom salivary IgG was detected had relatively high serum antibody titres (table VI).

Discussion

The interactivated whole virus hepatitis A vaccine used in this trial was well tolerated and highly immunogenic. Side effects were generally mild and transient and similar in nature and frequency to those observed with hepatitis B vaccines. The finding that the frequency of symptoms decreased with successive doses suggests that this vaccine did not induce a

TABLE VII—*Potential candidates for immunisation with hepatitis A vaccine in developed countries and seroprevalence of hepatitis A virus specific IgG*

Year	Potential candidates	Age range (mean) (years)	No tested	No positive (%)
1990	Medical students	19-26 (21)	33	2 (6)
1990-1	Service recruits	17-25 (19)	1334	90 (7)
1980	Intravenous drug abusers	18-48 (28)	89	46 (52)
1980	Male homosexuals	16-62 (30)	75	26 (35)
	Other travellers to hepatitis A endemic countries			
	Staff of children's day care centres			
	Sewage workers			

hypersensitivity reaction to any of its components.

One dose of vaccine alone induced a seroconversion rate of 97%, and all those immunised seroconverted after two doses. The interval between the first two doses may be reduced to two weeks (F Andre, seventeenth international congress of chemotherapy, Berlin, 1991); protection against hepatitis A, therefore, should be achieved by giving a primary course of two doses, two to four weeks apart. In travellers, however, if the interval between immunisation and departure is less than two weeks active or passive protection may be considered.

The antibody levels produced by the third dose of vaccine varied considerably among volunteers, and among men the geometric mean titre was significantly lower one month after the third dose with the shorter schedule. At 12 months this group-sex interaction had resolved, but the geometric mean titre in both men and women was significantly higher in group 2; at two years this difference was no longer significant. We cannot explain why men initially respond relatively poorly with the shorter schedule, but in the long term such differences are unlikely to affect efficacy of the vaccine.

The duration of the immune response after immunisation can be determined only by long term follow up studies. The need for a booster dose with hepatitis B vaccines is still under debate; no doubt hepatitis A vaccines will be the subject of similar discussions.

Protection studies are difficult to implement, and, although our study does not address the question of vaccine efficacy, the antibody responses in saliva and parotid fluid show qualitative differences between natural and vaccine induced immunity, which may be useful in discriminating between the two. Inactivated poliomyelitis vaccines, however, which are produced from an enterovirus with many similarities to hepatitis A virus, are protective, and they too produce little or no local immunity.[14] Furthermore, the inactivated hepatitis A vaccine used in this study has been shown to induce neutralising antibodies, with titres generally exceeding those after a single dose of human normal immunoglobulin,[15,16] a product of proved efficacy.[17] This vaccine might therefore be expected to protect.

To whom should the vaccine be given? In the United Kingdom notifications of hepatitis A to the Public Health Laboratory Service Communicable Disease Surveillance Centre have shown a progressive increase for each year since 1987, and the cumulative total of laboratory confirmed reports of the disease in 1990 was 7457.[18] Interestingly, however, only about 14% of cases are associated with a history of recent travel abroad,[4] and evidence from several centres in the United Kingdom suggests that hepatitis A virus is endemic and spreading in the community, particularly in deprived urban areas.[19]

Control of hepatitis A virus may be achieved with simple hygienic measures and passive immunoprophylaxis with human normal immunoglobulin, which, although safe and efficacious, is not without cost. Furthermore, it is a plasma product affording only short term protection and the injection may be painful. In addition, the protective efficacy of human normal immunoglobulin may decline with falling levels of immunity in developed countries. An increasing number of doses are issued annually, mainly to those travelling to areas of high endemicity of hepatitis A. Between 1987 and 1988 there was a 250% increase in the number of doses issued in the United Kingdom, and the total number issued in 1990 approached 600 000.[19]

In developed countries the vaccine would be particularly valuable to those who are at increased risk of acquiring hepatitis A, such as those who have to travel frequently or to spend extensive periods of time in areas of high endemicity. In young army service recruits, for example, the prevalence of immunity to hepatitis A is only 7% (N Cumberland, personal communication; table VII); hepatitis A vaccine would be valuable should they be posted abroad. Indeed, human normal immunoglobulin was not offered to British troops serving in the Gulf and at least eight cases of hepatitis A resulted (N Cumberland, personal communication). The United States troops, on the other hand, were protected with human normal immunoglobulin and no confirmed hepatitis A infections were recorded (J P Tomlinson, personal communication). Medical students would also benefit from a vaccine during their elective periods, and other target groups might include staff of day care centres, sewage workers, male homosexuals,[20] and intravenous drug abusers.[21]

Food handlers are often the source of outbreaks of hepatitis A. If a vaccine is to be given to this group, however, it must be shown to reduce excretion of hepatitis A virus significantly after challenge with live virus. Studies in animals are under way and preliminary results suggest that this may be the case.[22]

Where standards of hygiene are improving there tends to be an upward shift in the age incidence of hepatitis A with an increase in symptomatic cases, sometimes reaching epidemic proportions.[23,24] A vaccine given as part of the childhood immunisation programme is likely to be beneficial in these areas, but low cost and long term protection are essential. In this context a combined hepatitis A and B vaccine could be useful.

Unfortunately, high production costs and poor virus yield have made the new hepatitis A vaccine costly, which will limit its use in developing countries. Until these problems can be overcome a live vaccine, should one become available, may be more suitable. Nevertheless, in developed countries there is likely to be considerable demand for inactivated vaccines.

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Is *Helicobacter pylori* the cause of dyspepsia?

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Abstract

***Objective*—To determine the association between infection with *Helicobacter pylori* and dyspepsia.**

***Design*—Cross sectional study of dyspeptic subjects and age and sex matched controls identified by a questionnaire survey of all inhabitants aged 20-69. (Endoscopy, histological examination, and microbiological examinations of biopsies from the gastric mucosa were performed blind.)**

***Setting*—Population based survey in Sørreisa, Norway.**

***Subjects*—All 782 dyspeptic subjects (excluding those with a previous history of peptic ulcer, gall stones or kidney stones, and coronary heart disease) and controls were offered an endoscopy, of whom 309 dyspeptic subjects and 310 controls attended.**

***Main outcome measures*—Prevalences of endoscopic and histological diagnoses and of cultures positive for *H pylori*.**

***Results*—A high prevalence of positive cultures, increasing with age, was found in both dyspeptic subjects (48%) and non-dyspeptic controls (36%) (p=0·004). Positive cultures in both dyspeptic subjects and controls were strongly associated with histological gastritis (70%, 95% confidence interval 65·5 to 85·3; 60%, 52·7 to 67.7, respectively) and peptic ulcer (92%, 61·5 to 99·8; 64·1, 9·4 to 99·2, respectively). Only 3% of subjects with a histologically non-inflamed gastric mucosa had this infection (dyspeptic subjects 2%, 0·2 to 7·0; controls 4%; 1·2 to 8·8).**

***Conclusions*—The relation between dyspeptic symptoms and *H pylori* is dubious; *H pylori* seems to have a pathogenetic role in gastritis and may be a contributing factor but not a cause of peptic ulcer.**

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Introduction

Dyspepsia requires costly management despite lack of knowledge of its causes. The rediscovery by Warren and Marshall[1] of curved bacilli in the gastric mucosa which were related to gastritis[1-3] has recharged the discussion about the cause of dyspepsia. A strong association between *Helicobacter pylori* and gastritis and peptic ulcer disease has been shown in patient populations.[1 4-8] *H pylori* has been declared an aetiologic agent of gastritis and even the cause of dyspepsia, though this is disputed.[9-12] Studies on asymptomatic volunteers have shown high prevalences of *H pylori* infection,[4 13 14] of up to 47% in the age group 60 to 69,[14] but there is little evidence of its prevalence in healthy, normal populations and of the concurrence of *H pylori* infection and symptoms of dyspepsia. Only one study on the occurrence of *H pylori* in a general population has been published.[15] Population based data are mandatory in considering *H pylori* as a pathogenetic agent in gastritis and peptic ulcer disease and as a possible cause of dyspepsia.[6 16]

As part of a population based study we examined by endoscopy unselected subjects with dyspepsia and matched non-dyspeptic controls to determine the prevalence of *H pylori* infection and its relation to endoscopic and histological diagnoses.

Subjects and methods

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

All of the subjects answering positively to the first two questions: "Have you ever had abdominal pain of at least two weeks' duration?" and "If yes, was the pain located to the upper abdomen?" or the last question: "Have you ever had heartburn or acid regurgitation almost daily during at least one week?" were considered to have dyspepsia.

After exclusion of 89 dyspeptic subjects with a prior history of peptic ulcer, 15 with gall stones or kidney stones, and 33 with coronary heart disease the remainder were offered an endoscopy free of charge. Corresponding healthy, non-dyspeptic controls matched for sex and age within the same 10 year age group were randomly selected and offered an endoscopy. The controls reported that they had never experienced dyspeptic symptoms and also had never consulted their general practitioner with dyspepsia. Of 2027 subjects invited, 1802 (88·9%) returned the questionnaire. Of 782 subjects invited to endoscopy, 619 (79·2%) (309 dyspeptic subjects and 310 non-dyspeptic controls) had endoscopy, all within one month after returning their questionnaires. A detailed description of the methods has been published elsewhere.[17] The study was approved by the regional committee for medical research ethics.

ENDOSCOPY

All endoscopies were performed by BB, who is a trained endoscopist. He was "blinded" in the sense of not knowing whether he was examining a dyspeptic or a non-dyspeptic subject. Endoscopic findings were classified according to criteria described by Savary and Miller (oesophagitis),[18] Johnsson *et al* (hiatus hernia),[19] Myren and Serck-Hanssen (endoscopic gastritis and gastroduodenal reflux),[20] Nesland and Berstad (erosive