A celebration of British gastroenterology, 1987–97

The President and Council of the British Society of Gastroenterology invited Gut to help celebrate the Society's Diamond Jubilee. I and the Associate Editors put two proposals to Council which were approved and have now found their way into this special supplement of the Journal. The material in this supplement summarises the findings of two research projects. The first project was to identify systematically the most cited papers in Gut during the past decade. Tom MacDonald led this project and used the Science Citation Index database accessed through the Bath Information and Data System (BIDS) to identify the most cited paper for each year of the decade. There are one or two interesting outcomes. Firstly, this collection of papers does not overlap in any way with Roy Pounder's series in Collection of Scientific Papers 1987–97 which was culled from a larger self-selected group of papers nominated by BSG members. Thus, work which we judged ourselves to be our best efforts (as it relates to papers published in Gut) are not necessarily those that are widely recognised, at least by citation, by the larger scientific community as a whole. Secondly, I suppose it should be no surprise that Helicobacter pylori continued to take the limelight throughout the decade. Other highly cited papers included those on non-steroidal inflammatory drugs, pro-inflammatory cytokines in inflammatory bowel disease, malignancy in coeliac disease, and the pathogenesis of gastro-oesophageal reflux.

What is the point of this exercise, one might ask? For the investigator it does provide some sort of index of 'hot topics' and areas of intense research activity, albeit a retrospective review. Whether this should or can in any way influence our submissions for RAE 2000 might be mused upon. For those of us driving Gut towards the millennium, it also provides food for thought. While we continue to strive to attract the most innovative and highest quality research papers in gastroenterology and hepatology, we need to take into account indexes of success such as the impact factor of the Journal, which is based on the frequency at which our papers are cited in the literature. This kind of analysis is perhaps one way in which we can derive information which might guide the editorial process.

The second section of the Diamond Jubilee supplement is a piece of research which aims to examine the progress of gastroenterology and hepatology in the United Kingdom during the past 10 years, and attempts to project forward to define the growth areas of the future. This was qualitative research using the semi-structured interview approach. We selected a number of topics which we thought would be important to gastroenterologists and hepatologists, and paired these with BSG members who were knowledgeable in their field and who would be able to 'look back and look forward'. The interviews cover peptic ulcer disease (George Misiewicz), inflammatory bowel disease (John Lennard-Jones), functional bowel disorders (David Thompson), endoscopy (Christopher Williams), nutrition (David Silk), liver disease (Roger Williams), and molecular gastroenterology (Alex Markham). In addition, we have an interview with Hermon Dowling, the 1996/97 President of the BSG, who reflects on the current and future health of the Society and another with Sir Francis Avery Jones who reflects on Sir Arthur Hurst and the beginnings of the BSG and looks forward with great wisdom on one of his major current interests, the relation between food and the gut. These are highly selective personal views and cannot be regarded in the same way as a randomised, double-blind, placebo-controlled trial! However, the information that they provide and the concepts and ideas contained therein are of value and may provide useful insights for our Society and the research community in gastroenterology and hepatology in the future.

Review of the past 10 years provides an interesting summary of the outstanding progress that has been made in understanding disease pathogenesis, its genetic basis and the new therapies that have followed. Predictions for the future should inform and perhaps focus our own research aspirations in the future. Common themes emerge from a number of interviews. The continued need for research training despite the move towards a highly structured, more rapid clinical training as a specialist registrar. The concept of the clinician/scientist seems to survive into the next millennium and the need to promote molecular-based research programmes in gastroenterology and hepatology is emphasised in most of the interviews. The BSG should have a pivotal role in promoting high quality basic and clinical research in the UK, liaising with funding agencies and the Department of Health, possibly co-ordinating clinical programmes nationwide.

I would like to thank all of those who have given their time to the production of this supplement. It has been an informative and enjoyable process and I hope the product will serve not only as a 60 year milestone for the BSG but perhaps provide some inspiration for the future.

MICHAEL J G FARTHING
February 1997
Top three in *Gut*, 1985–1994

1985

1986

1987

1988

1989

1990

1991


1993


1994


Thomas T MacDonald

Citation index has become the SI unit of academic success and is the yardstick which can make or break academic careers. It is no longer sufficient to publish—publications must be in high impact factor journals. The impact factor is the value obtained when the total number of times papers have been cited is divided by the number of papers a journal publishes in the previous two years. It is assumed that papers in journals with high impact factors reflect the highest quality research. By and large this is true, but as an impact factor is an average, it disguises the fact that a few papers in low impact factor journals get cited a lot and that some papers in high impact factor journals are rarely cited. It is also dangerous to ascribe small differences as meaningful; there is no difference between 2.5 and 3, but between 2.5 and 10 there is! In some specialties, for example, paediatrics, even the best journals have relatively low impact factors (<3). This does not mean that paediatric research is of low quality, instead it means that paediatricians do not publish their best papers in paediatric journals. Despite the flaws and its many critics, the impact factor of the journals in which one publishes is widely used to determine the quality of research. This has a direct effect on ability to generate external funding and is taken into account in the UK when assessing the research rankings of British universities. The higher the research rating, the more money the institution gets. In November 1995, Gut’s impact factor was 3.023, ranking it third amongst the specialised journals in gastroenterology and hepatology.

To obtain more detailed information on how many times individual articles in Gut were cited, we analysed the citation indexes of every article published between 1985 and 1994. We were especially interested in the types of papers cited (reviews, leading articles, original research, case reports) as well as the topic (inflammatory bowel disease, cancer, etc.).

Methods
The work was carried out in December 1996 using the Science Citation Index database accessed through the Bath Information and Data System (BIDS). This system uses the name and initials of the first author of the paper, the journal and the year as the basis for the search. It cannot distinguish between an author who publishes a single article in Gut in a given year and someone who publishes a number of articles in that year. Thus, Smith J. may have published one paper in Gut in 1989 with 300 citations and Jones A. published three papers with cumulative citations of 300. To solve this problem, the articles in which the work was cited were downloaded and citations manually ascribed to each paper. The accuracy of the database depends on the accuracy of the citation in the published paper. Names, year and volume numbers are often misquoted; however, in practice this does not cause an insurmountable problem. It was decided to subdivide the papers by year of publication as the longer a paper is in the literature, the more chance it has to accumulate citations (or be forgotten).

Results
Between 1985 and 1994, 2854 articles were published in Gut. In 1985, 216 articles were published and this increased steadily, reaching 359 in 1994. There was a clear trend for the average number of citations per article to decrease with time, and in recent years where even the most cited articles often had less than 100 citations, the article selected often had only one or two more citations than six or eight others. There is, therefore, an element of rough justice in choosing the most cited article in some years and this was particularly the case in 1990–1992. In the earlier years studied, there were usually two to three papers well ahead of the others, by a margin of 50 to 100 citations.

The front pages of the most cited articles each year are shown. It is clear that a single micro-organism dominates the list. In five of the 10 years studied, articles on Helicobacter pylori were the most cited, and the most cited article of all in Gut between 1985 and 1994 was from Rathbone and colleagues in 1986 on antibody responses to H pylori, achieving almost 400 citations. Shortage of space precludes inclusion of the data, but if one examines the three most cited articles each year, then out of 30, 14 mention H pylori. Other studies on the stomach are also amongst the most cited. In 1987, Armstrong and Blower published a key paper on NSAIDs and peptic ulceration and is the most cited that year (318 citations). In 1985 Collier and Pain published a paper on NSAIDs and peptic ulcer perforation with 222 citations (second most cited) and McCormack et al published the third most cited paper (199 citations) that year on gastric lesions in portal hypertension. In 1987, Jones et al published the third most cited paper with 175 citations on a meta-analysis of the best anti-secretory drugs. The most cited paper in 1988 was by Dent and colleagues on lower oesophageal sphincter incompetence in reflux.

Malignancy also featured highly. In 1988 a paper by Gyde and colleagues (108 citations) on colorectal cancer and ulcerative colitis was the second most cited paper and the most cited paper (176 citations) in 1989 was by Holmes et al about malignancy in coeliac disease. In 1990 the second most cited article was by John
Lennard-Jones and colleagues\(^2\) (86 citations), also on cancer in ulcerative colitis.

In 1990 the most cited paper was by Liggansky and colleagues (125 citations) on interleukin-1 in inflammatory bowel disease (IBD). However, another paper on the same topic by Yashwan Mahida \textit{et al.}\(^3\) in 1989 on the same topic had more citations but was only the second most cited article that year. Another paper on cytokines in IBD by Brynskov \textit{et al.}\(^4\) was the third most cited in 1992 (72 citations).

With the exception of an article by Moss and Calam in 1992 on the relation between \textit{H pylori} and peptic ulcers, leading articles were poorly cited, as were case reports and experimental studies in animal models. The controversial nature of the cause of Crohn’s disease also featured and the paper by Sanderson and colleagues in 1992\(^5\) on \textit{Mycobacterium tuberculosis} received 72 citations and was the second most cited article that year.

**Conclusions**

1985–1994 was clearly the decade of \textit{Helicobacter pylori}. The large numbers of papers published on this topic in \textit{Gut} and the large number of citations they received shows that they have made a significant impact in gastroenterology. The 30 papers representing the three most cited in each year were all clinical papers, and overall, experimental studies in animals were poorly cited. It would probably be wrong to conclude now that if one wished to make an impact in gastroenterology, one should work on \textit{H pylori} in patients as that advice seems to have been taken by most gastroenterologists anyway.

With time, the difference in the number of citations between the leaders and the rest increased, suggesting that certain articles had staying power and were cited many years after their publication. The Institute for Scientific Information actually calculates this and gives an estimate of cited half-life, which does not correlate with impact factor. This is presumably because high impact factor journals publish articles in hot areas which are likely to be superseded faster.

This analysis was also able to identify those articles which were not cited. To avoid embarrassing many of the senior figures in gastroenterology, these will not be highlighted.

Campylobacter pyloridis in peptic ulcer disease: microbiology, pathology, and scanning electron microscopy

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Summary After the recent successful isolation of spiral organisms from the stomach this paper presents the bacteriological and pathological correlation of gastric antral biopsies from 51 patients endoscopically for upper gastrointestinal symptoms. Campylobacter pyloridis was cultured from 29 patients and seen by either silver staining of the biopsy or scanning electron microscopy in an additional three. The organism was cultured from 23 of the 33 (69%) patients with peptic ulcer disease and from within this group 17 (80%) of the 21 patients with duodenal ulceration. It was cultured only once from the 12 normal biopsies in the series but from 27 of the 38 (71%) biopsies showing gastritis. C pyloridis was also cultured from five out of seven of the 14 endoscopically normal patients, who despite this had biopsy evidence of gastritis. It was the sole organism cultured from 65% of the positive biopsies and scanning electron microscopy invariably revealed it deep to the surface mucus layer. C pyloridis persisted in the three patients with duodenal ulcers after treatment and healing. The findings support the hypothesis that C pyloridis is aetologically related to gastritis and peptic ulceration though its precise role still remains to be defined.

The presence of spiral bacteria on gastric mucosa has been noted by histopathologists for many years.1 Fresh impetus to these observations and to the search for the aetiology of peptic ulcer disease has been given by the culture of these organisms and the demonstration of their association with gastritis and duodenal ulcer.2-4 Other communications5-7 have upheld these initial findings. The provisional name of Campylobacter pyloridis has been assigned to the new organism.3 8

This paper presents a prospective study on a series of patients with peptic ulcer disease, designed to look at the incidence of this new organism in the stomach and to try and shed light on whether it is a pathogen or not.

Methods

Patients and Endoscopy

The study comprised 51 patients presenting to the gastroenterology clinic at Northwick Park Hospital who were divided into the following groups: acute duodenal ulcer 21, healed duodenal ulcer two, chronic gastric ulcer seven, healed gastric ulcer three, gastritis two and pernicious anaemia two. There was also a group of 14 patients with dyspeptic symptoms but without endoscopic abnormality.

At endoscopy three mucosal biopsies were taken from each patient from within 5 cm of the pylorus. These were submitted in separate containers, one for bacteriological culture, and one each for examination by light and scanning electron microscopy (SEM). The 51 patients provided 55 biopsy samples as four patients had follow up biopsies. The diagnoses were coded and known only to the endoscopist (AS) until the end of the study.

Histopathology and Scanning Electron Microscopy

The biopsies for light microscopy were fixed in 10% formalin, routinely processed to paraffin and 3 μm sections cut. Sections from all 55 biopsies were stained with haematoxylin and eosin and by the
Alimentary tract and pancreas

Systemic and local antibody responses to gastric *Campylobacter pyloridis* in non-ulcer dyspepsia

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**SUMMARY** Antibody titres to *Campylobacter pyloridis* in serum and gastric juice were estimated by an enzyme linked immunosorbent assay (ELISA) to whole organisms obtained from bacterial culture in 39 patients with non-ulcer dyspepsia. Whereas 20 of the 21 patients with chronic gastritis had gastric *C. pyloridis*, 17 patients with no *C. pyloridis* had normal histology in the gastric antrum and body. Significantly raised serum IgG and IgA antibody titres to *C. pyloridis* were found in colonised patients with gastritis. Patients with raised IgG antibody to *C. pyloridis* were also shown to have significantly raised titres to other Campylobacter species, suggesting antigenic cross reactivity. Gastric juice antibodies were also studied and IgA titres to *C. pyloridis* were detected in a proportion of patients with gastritis, together with low levels of IgM, but no IgG.

The presence of spiral organisms in the stomach has been noted on a number of occasions dating back to 1938. It was only recently, however, that the significance of gastric spiral organisms was recognised by Warren and Marshall who identified the previously detected curved bacilli on the gastric epithelium of the majority of patients with active chronic gastritis by the Warthin-Starry silver stain. Morphologically, and in respect to their atmospheric requirements and DNA base composition, these organisms are most closely related to the genus Campylobacter. Reports from a number of workers have all confirmed the presence of these organisms in the majority of patients with gastritis. The organism was originally described as a 'Campylobacter-like organism' (CLO) but has now been formally named *Campylobacter pyloridis*. It remains to be seen whether *C. pyloridis* is involved in the pathogenesis of chronic gastritis, or is merely a commensal organism.

Little is known of host defences to *C. pyloridis*, either at the systemic or the local level. Jones et al. studied circulating antibody to *C. pyloridis* by agglutination and complement fixation techniques. They showed raised titres in *C. pyloridis* positive patients, but did not analyse the response by antibody class, and hence shed little light on the host response.

To further characterise the serum and local antibody response, we have studied circulating and gastric juice antibodies to *C. pyloridis*, with particular reference to antibody class. In addition, we compared serum antibody titres with other strains of gastric *C. pyloridis* isolated from different patients, and to other Campylobacter species.

**Methods**

**PATIENTS**

Thirty nine patients (21 men, mean age 41 years) without peptic ulceration were studied. Endoscopic biopsies were obtained for histology and bacterial isolation and culture. Serum and fasting gastric juice were collected for antibody assay.

**ENDOSCOPY**

The examination was carried out by one endoscopist using an Olympus GIF-T fiberoptic gastroduodenoscope, sterilised between patients with Detox (Reckitt & Colman). Fasting gastric juice samples were collected and stored at -20°C. Biopsies were taken from the gastric body on the greater curve and the antral floor. The biopsies for histology were immediately fixed in 10% buffered formalin. An additional antral biopsy was also placed in Stuart's...
Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration

C P ARMSTRONG AND A L BLOWER

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SUMMARY Two hundred and thirty five consecutive patients with a life threatening complication of peptic ulceration, who either died or required emergency surgery, have been studied over a 36 month period. Seventy eight of these high risk patients died; 25 at home, 19 in hospital without surgery and 34 postoperatively. Ninety eight patients had bleeding ulcers, 132 perforated ulcers and five had both bleeding and perforated ulcers. One hundred and forty one of these 235 patients (60%) were taking a non-steroidal anti-inflammatory drugs (NSAID) and the individual agents have been listed. The overall incidence of NSAID use in a hospital control group was 9-9%. The first sign of an ulcer was a life threatening complication in 58-2% of patients taking a NSAID. Nearly 80% of all ulcer related deaths occurred in patients using an anti-inflammatory agent. Patients using these drugs were older, with more pre-existing medical conditions and had larger ulcers than those not taking NSAIDs. The mortality associated with a peptic ulcer complication in patients taking a NSAID was more than twice that in patients with no such drug history. There appears to be a relationship between the development of a life threatening complication of peptic ulceration and NSAID ingestion. Much of the associated mortality and morbidity may be potentially avoidable.

There is evidence of a recent reduction in the number of elective operations for chronic peptic ulcer. Nevertheless, peptic ulceration remains a serious problem and was responsible for nearly 14 000 deaths in England and Wales over the years 1982-4. Of these ulcer related deaths 7000 were associated with bleeding and 5000 with perforation and three-quarters of the mortality occurred in patients over the age of 70 years. It has recently been reported that the incidence of perforated peptic ulcer is increasing in elderly men and women in contrast with a decrease in the younger age groups. Non-steroidal anti-inflammatory drugs (NSAID) have been associated both with the development of peptic ulceration and the life threatening complications of haemorrhage and perforation. As 22 million prescriptions for NSAIDs were issued in the United Kingdom in 1985 their relationship to peptic ulceration requires urgent clarification. The aim of this study was to relate NSAID ingestion to all cases of peptic ulceration with perforation or bleeding who either died or underwent emergency surgery in a given area. We have selected only patients at high risk and the figures presented do not relate to all bleeding ulcers.

METHODS

PATIENTS

This study analyses a consecutive series of 235 patients who either died as a result of, or required emergency surgery for, bleeding or perforation of a benign peptic ulcer between January 1983 and December 1985 (36 months). Information from the first six months was obtained by retrospective case note examination and from the last 30 months in a prospective manner. Patients were from the South Cheshire area which is served by Leighton Hospital and provides all acute services for a population of approximately 250000. Those patients who died suddenly at home or in hospital before operation
Mechanisms of lower oesophageal sphincter incompetence in patients with symptomatic gastrooesophageal reflux

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SUMMARY

Patterns of lower oesophageal sphincter (LOS) function associated with the onset of 644 reflux episodes were recorded and analysed in 67 patients referred for evaluation of gastrooesophageal reflux (GOR). Patients were studied recumbent, for one hour before and four hours after a standard meal. Transient LOS relaxation was the most prevalent mechanism and overall accounted for 82% of reflux episodes. With increasing severity of oesophagitis, absent basal LOS pressure became a progressively more common mechanism, accounting for 23% of episodes in the patients with severe oesophagitis. Patients commonly exhibited more than one mechanism. The timing of most (69%) LOS relaxations associated with reflux was not compatible with triggering by swallowing. Prolonged transient LOS relaxations were associated with inhibition of oesophageal peristalsis suggesting that this response is produced by neural inhibition. This study suggests the primary importance of transient LOS relaxations as the cause of GOR across the spectrum of severity of reflux disease.

For many years gastrooesophageal reflux (GOR) was generally believed to result from lower oesophageal sphincter (LOS) incompetence caused by defective basal LOS tone.1,2 This concept, however, fails to account for the substantial proportion of patients with reflux disease in whom resting LOS pressure is normal.3 A recent study has shown that GOR in normal subjects occurs almost exclusively as a result of transient LOS relaxation, rather than from defective basal LOS pressure.4 In a subsequent study of 10 selected patients with erosive peptic oesophagitis, transient LOS relaxation accounted for 65% of reflux episodes, the remainder of reflux episodes occurring during prolonged periods of absent or low basal LOS pressure.5 The aims of the present study were to: (a) investigate possible variation in the mechanisms of GOR within a large group of patients exhibiting a spectrum of severity of reflux disease: and (b) analyse in detail, patterns of oesophageal motility associated with reflux events in an effort to gain insight into the mechanism of transient LOSRs.

Methods

STUDY GROUP

The study protocol outlined below was approved by the Ethical Review Committee of Flinders Medical Centre in March 1977. The patients included in the study were referred because they represented a problem in clinical management. The reasons for referral included troublesome or atypical symptoms, atypical oesophageal ulceration, and preoperative assessment for antireflux surgery. Patients with a previous vagotomy, gastric resection, gastroenterostomy, or antireflux surgery were excluded. This report describes the findings in 67 patients in whom technically satisfactory oesophageal manometric and pH recordings were obtained. Studies in 23 other patients were unsatisfactory because of technical failure of pH electrodes, difficulties with intubation, or failure of the subject to complete the...
Malignancy in coeliac disease – effect of a gluten free diet

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SUMMARY Two hundred and ten patients with coeliac disease previously reported from this unit were reviewed at the end of 1985 after a further 11 years of follow up. The initial review at the end of 1974 could not demonstrate that a gluten free diet (GFD) prevented these complications, probably because the time on diet was relatively short. The same series has therefore been kept under surveillance with the particular aim of assessing the effects of diet on malignancy after a further prolonged follow up period. Twelve new cancers have occurred: of which one was a carcinoma of the oesophagus and two lymphomas. Thirty nine cancers developed in 38 patients and of 69 deaths, 33 were the result of malignancy. A two-fold relative risk (RR) of cancer was found and was because of an increased risk of cancer of the mouth and pharynx (RR=9.7, p<0.01, 95% confidence interval (CI)=2.0–28.3), oesophagus (RR=12.3, p<0.01, CI=2.5–36.5), and of non-Hodgkin’s lymphoma (RR=42.7, p<0.001, CI=19.6–81.4). The results indicate that for coeliac patients who have taken a GFD for five years or more the risk of developing cancer over all sites is not increased when compared with the general population. The risk is increased, however, in those taking a reduced gluten, or a normal diet, with an excess of cancers of the mouth, pharynx and oesophagus (RR=22.7, p<0.001), and also of lymphoma (RR=77.8, p<0.001). A significant decreasing trend in the excess morbidity rate over increasing use of a GFD was found. The results are suggestive of a protective role for a GFD against malignancy in coeliac disease and give further support for advising all patients to adhere to a strict GFD for life.

There are several reports of an association between steatorrhoea and intestinal lymphoma which have been recently summarised. The malabsorption was attributed in the early literature to lymphatic obstruction by enlarged mesenteric glands but abnormalities in the small intestinal mucosa were also thought to play a part. In reports up to 1961, the steatorrhoea in every case was considered to occur secondary to the lymphoma.

In 1962, Read and his colleagues from Bristol suggested that lymphoma was a complication of coeliac disease in which the mucosal abnormality was a premalignant condition. They produced further evidence for this idea, while in Birmingham the prevalence of lymphoma was shown to be statistically increased in coeliac disease and idiopathic steatorrhoea. This report also drew attention to the increased risk of developing gastrointestinal carcinoma in general and oesophageal carcinoma in particular. Cancer of the small bowel is also a recognised association and this observation was confirmed by the British collaborative study of coeliac disease and malignancy.

At the end of 1974 a series of 210 patients with coeliac disease from the Gastroenterology Unit at the General Hospital, Birmingham, was analysed with regard to malignant complications and the effect on these of a gluten free diet (GFD). A statistically significant increase in deaths from cancer occurred in the whole series and in men and women separately.
Role of interleukin 1 in inflammatory bowel disease – enhanced production during active disease

M Ligumsky, P L Simon, F Karmeli, D Rachmilewitz

Abstract
Interleukin 1 is a polypeptide cytokine produced by various cell types and has been shown to have a major role in inflammatory and immunological responses. In experimental colitis it proved to be a dominant mediator and a reliable marker of inflammation. The aim of the present study was to determine the extent of production and release of interleukin 1 from colonic mucosa of patients with active untreated inflammatory bowel disease. Colonic mucosal biopsy specimens were obtained during colonoscopy from 17 patients with ulcerative colitis, eight patients with Crohn's disease of the colon, and 16 normal control subjects. Interleukin 1 content was determined in fresh and 24 hour organ cultured mucosa as well as in cultured medium. Interleukin 1 content and release were significantly higher in the inflamed mucosa compared with that of control subjects. Prednisolone inhibited interleukin 1 release in a dose dependent fashion. We conclude that colonic mucosal interleukin 1 content and production is significantly raised in active inflammatory bowel disease and may have a role in the pathogenesis of the inflammatory response. Pharmacological suppression of tissue interleukin 1 production may have a beneficial therapeutic effect.

Interleukin 1 is a polypeptide cytokine produced by various tissue cells¹ and has a variety of biological properties.² It is a key mediator that is released by monocyte macrophages in inflammatory and immunological responses.³ Interleukin 1 acts locally by releasing prostaglandins, thromboxane, and platelet activating factor from the inflammatory cells, and systemically as a circulating hormone, it induces fever and the production of acute phase reactants by the liver.⁴,⁵

Since infiltration of inflammatory cells in the gut wall is a feature of inflammatory bowel disease, interleukin 1 may have a role in its pathogenesis. Recently, peripheral blood mononuclear cells obtained from patients with Crohn’s disease were shown to produce in vitro high quantities of interleukin 1 compared with normal control cells,⁶ and enhanced production of interleukin 1-beta was shown in colonic mononuclear cells isolated from patients with inflammatory bowel disease.⁷ Moreover, mucosal interleukin 1 values were reported by us to be increased in two models of experimental colitis – in trinitrobenzene sulfonic acid colitis induced in rats⁸ and in a rabbit model of acute colitis induced by enteropathogenic Escherichia coli.⁹ In both models, mucosal interleukin 1 was found to be the most sensitive marker of colonic inflammation.

The aim of the present study was to determine the interleukin 1 content in fresh and cultured inflamed colonic mucosa obtained from patients with active ulcerative colitis and Crohn’s disease of the colon and to assess the effect of drugs on its release during 24 hours of culture.

Materials and methods

Studies with mucosal specimens
Mucosal tissue specimens were obtained during fiberoptic colonoscopy from inflamed sites in the recto-sigmoid colon of patients with untreated active ulcerative colitis and Crohn’s colitis, as well as from normal control subjects without any abnormalities in their colon. The major reasons for colonoscopy in the control group were non-specific abdominal complaints, bleeding, haemorroids, and occult blood in the stool. Biopsy specimens obtained from the control groups did not show any histological abnormality. The diagnosis of ulcerative and Crohn’s colitis was established according to clinical, endoscopic, pathological, and radiological criteria. In all patients with ulcerative colitis clinical activity was manifested by bloody diarrhoea and verified histologically by the presence of mucosal ulceration, crypt abscesses, and infiltration with inflammatory cells. The mean (SE) clinical activity index in patients with Crohn’s colitis was 230 (48). Histological examinations in these patients showed mucosal ulcerations and mononuclear infiltration of the mucosa. No granuloma were found in any biopsy specimens examined. No subjects, controls, or patients, had received any medication for at least two weeks before the biopsy specimens had been obtained. The age and sex of the subjects examined are presented in Table I. The study protocol was approved by the local hospital’s Helsinki committee. Tissue specimens were cultured (37°C, 5% CO₂, 95% air) for 24 hours, as described earlier.¹⁰ In brief, the tissue was placed on a metal grid over the central well of the culture dish (Falcon) containing the culture medium which consisted of 0.7 ml RPMI 1640 (BioLab, Israel) containing penicillin (100 U/ml) and streptomycon (100 μg/ml). In some experiments mucosal biopsy specimens obtained from the same patient were also incubated for one, two, three, and four hours. Each culture dish contained three specimens. Fresh and cultured specimens, average weight 10 mg, were homogenised with a polytron homogeniser (Kinematic, Kriens-Lu, Switzerland) for 20 seconds at a speed grade of 6 in 0.5 ml 50 mM Tris HCl buffer, pH 7.4, containing 100 mM...
Acute Helicobacter pylori infection: clinical features, local and systemic immune response, gastric mucosal histology, and gastric juice ascorbic acid concentrations


Abstract
The symptomatology of a case of acute infection with Helicobacter pylori is described, together with the accompanying changes in gastric mucosal histology, local and systemic humoral immune response, and gastric ascorbic acid concentration. The patient was an endoscopist, previously negative for the carbon-14 urea breath test, who had a week of epigastric pain and then became asymptomatic. H pylori was detected by culture of antral biopsy specimens and was still present after 74 days. Five days after infection the histological findings showed acute neutrophilic gastritis; by day 74 changes of chronic gastritis were evident. The patient seroconverted by IgG enzyme linked immunosorbent assay by day 74, but a mucosal IgM and IgA response was evident as early as day 14. Infection was accompanied by a transient hypochlorhydria but a sustained fall in gastric juice ascorbic acid concentration.

It is now widely accepted that Helicobacter pylori is the cause of chronic gastritis, and a large proportion of the world population is chronically infected with this organism. The only descriptions of illness accompanying the onset of infection come from two experimental infection studies,2 3 retrospectively from gastric intubation studies in which iatrogenic infection occurred,4 5 and from a single case report of spontaneous infection.6 These may not be representative. We have had the serendipitous opportunity to examine in detail the symptoms, changes in local and systemic immune response, and gastric histology accompanying a further case of spontaneous infection with this organism. We have also been able to determine gastric juice ascorbic acid concentration changes before and after infection. Ascorbic acid is thought to be protective against gastric cancer and is secreted by the normal stomach. This secretion is impaired in the presence of H pylori associated chronic gastritis.7 8

Case report
CLINICAL FEATURES
A 30 year old gastroenterology research fellow (GMS) was engaged in research which involved aspirating and handling gastric juice. A "C-urea breath test had been negative 2-5 years previously. Over the course of an evening he developed severe epigastric pain which occurred in cramping waves lasting 15 to 30 seconds at intervals of a couple of minutes. On the first day he had mild headache and malaise but remained afebrile. He had occasional mild nausea but did not vomit. The pains woke him every night between 3.00 am and 5.00 am. They were transiently exacerbated but then relieved by eating. The symptoms began to ease on day 5 and had completely resolved by day 7.

ENDOSCOPIC FINDINGS
Upper gastrointestinal endoscopy on day 5 showed only gastric erythema and a gaping pylorus. Aspirated gastric juice was neutral with a pH of 7.0. On day 14 gastric erythema was still present but less pronounced, and gastric juice had a pH of 7.5. At day 74 endoscopic appearances were within normal limits, and aspirated gastric juice was acid with pH 2.

MICROBIOLOGICAL FINDINGS
Two and a half years before the illness a "C-urea breath test had been completely negative. On day 5 a biopsy urease test (CLOtest, Delta West, Australia) was negative after one hour but positive after 24 hours' incubation, and H pylori was successfully cultured although growth was scanty. On day 14 both biopsy urease test and culture were negative. At day 74 a biopsy urease test was negative but H pylori was again successfully cultured. A "C-urea breath test (Europa Scientific, Crewe, England) was positive at day 91 and day 342.

Figure 1: Antral biopsy on day 5. The lamina propria of the mucosa is infiltrated by moderate numbers of inflammatory cells largely comprising neutrophil polymorphonuclear leucocytes. These infiltrate the surface epithelium, which is appreciably degenerate and shows cellular exfoliation. Haematoxylin and eosin. Original magnification x64.
Helicobacter pylori and peptic ulcers: the present position

We are currently at a curious point in the evolution of treatment for peptic ulcer. On one hand it has been discovered that eradication of Helicobacter pylori offers an excellent solution to the problem of duodenal ulcer relapse. On the other hand, most clinicians still choose to treat ulcers with regimens that do not offer this benefit. This could be dismissed as 'natural conservatism' or 'healthy scepticism' but the issue seems to be more profound. A doctor wishing to accept that H pylori and its eradication is important is immediately confronted with unresolved problems. Firstly, we have come to expect rational explanations, but some information on H pylori seems confused and in particular there is no consensus on how it causes ulcers. Secondly, there is no general agreement on how H pylori should be eradicated. This review discusses some of these problems and how they may be resolved.

The discovery: eradication of H pylori prolongs remissions
In 1981 Martin et al were surprised to find that duodenal ulcers stay healed for considerably longer after treatment with tri-potassium di-citrate bismuthate (De-Nol) than after H2 antagonists. H pylori was first cultured in 1983 and was identified in about 90% of patients with duodenal ulcer disease compared with a minority of control subjects.

Furthermore, De-Nol had anti-H pylori activity both in vivo* and in vitro. For some time, the connection between these observations was not generally accepted. It was noted that some bismuth remained in the body for up to four months after De-Nol treatment and that bismuth produces non-H pylori related benefits such as prostaglandin mediated cytoprotection. Another idea was that H2 antagonists might actually shorten remission by producing rebound hypersecretion of acid/pepsin, but there is little evidence to support this. Recent findings have established that H pylori does have a major effect on relapse. The addition of antibiotics to De-Nol increases eradication from about 20% to about 80% and produces a further considerable prolongation of remission. Remissions last a year or more if H pylori is eradicated compared with only about four months if it is not. Furthermore, recurrence after eradication is almost always preceded by recolonisation with H pylori.

Unresolved aspects of H pylori and duodenal ulcer disease

WHAT ARE THE RESPECTIVE ROLES OF H PYLORI AND ACID/PEPSIN?
Recurrence of duodenal ulcer disease is prevented by either eradication of H pylori or suppression of acid secretion. Apparently both acid/pepsin and H pylori are required to cause duodenal ulcers. Ulcers result where luminal attack exceeds mucosal resistance, but this may be an over simplification. Acid/pepsin clearly provides the luminal attack and H pylori probably reduces mucosal resistance, but the bacteria may also directly attack the epithelium.

HOW DOES H PYLORI CAUSE ULCERS IN THE DUODENUM?
Theories are broadly divided according to whether the proposed mechanism starts in the duodenum itself or in the stomach. While considering how H pylori causes ulcers, it is also important to consider why it does not have this effect in most people? The prevalence of H pylori increases with age, but at any time of life it is considerably above that of duodenal ulcer disease. For example, by the age of 50 years most of the population have H pylori but only about 10% have duodenal ulcers. This discrepancy may be viewed in terms of 'the seed or the soil' - are there ulcerogenic strains of H pylori, susceptible individuals, or both?

Duodenal mechanisms
It was initially difficult to understand how H pylori, which only colonised gastric type epithelium, might cause local damage within the duodenum. This is explained by the presence of patches of gastric metaplasia in the duodenum of patients with duodenal ulcer disease. It has been estimated that gastric metaplasia is present in about 90%, and is colonised with H pylori in about 50% of patients with duodenal ulcer disease, but only present in 5 to 30% of non-ulcer H pylori colonised persons. This raises the question of what causes gastric metaplasia? In man it is associated with acid hypersecretion and may be reduced after prolonged suppression of acid. In animals it has been induced experimentally by chronic stimulation of gastric acid secretion. However, gastric metaplasia is probably a non-specific response to injury. A similar phenomenon occurs in Crohn’s disease, in association with local epidermal growth factor production so an as yet unidentified insult could be responsible for gastric metaplasia in duodenal ulcer disease. Patches of metaplasia may well reflect the sites of previous ulcers but what causes the first ulcer?

Having colonised the duodenum, H pylori may cause ulcers by provoking inflammation or by releasing an ulcerogenic toxin. The nature of the inflammatory response in the duodenum has so far received little attention. Prostaglandins and platelet activating factor may be involved. Some results support the idea that certain types of H pylori are more...
Amoxicillin plus omeprazole versus triple therapy for eradication of Helicobacter pylori in duodenal ulcer disease: a prospective, randomized, and controlled study

J Labenz, E Gyenes, G H Rühl, G Börsch

Abstract

Treatment with amoxicillin and omeprazole resulted in encouraging Helicobacter pylori eradication rates in pilot studies that included medium term follow up. These results were evaluated in a prospective, randomised and controlled study. Forty patients with active duodenal ulcer disease and H pylori colonisation of the gastric mucosa were randomly assigned to receive either omeprazole (20 mg twice daily) and amoxicillin suspension (500 mg four times daily) for two weeks (group I) or bismuth subsalicylate (600 mg three times daily), metronidazole (400 mg three times daily), tetracycline (500 mg three times daily), and ranitidine (300 mg in the evening) for two weeks (group II). Study medication was followed in both groups by a four week treatment course with 300 mg ranitidine up to the final examination. One patient from each group was lost to follow up. H pylori was eradicated in 78.9% of group I and 84.2% of group II (p=1.00). All ulcers in patients on omeprazole plus amoxicillin healed but in the triple treatment group four patients had residual peptic lesions after six weeks (ulcer healing rate: 78.9%, p=0.11). Complete pain relief occurred after a median duration of 1 day in group I and of 6 days in group II (p=0.03). There were no major complications in either group but minor side effects were more frequently recorded in patients on triple therapy (63.2% v 15.8%, p<0.01). In conclusion, two weeks of treatment with omeprazole plus amoxicillin is as good as triple therapy plus ranitidine in eradicating H pylori but seems better with regard to safety, pain relief, and ulcer healing. Thus, amoxicillin plus omeprazole should be recommended as the treatment of choice in eradicating H pylori in patients with duodenal ulcer disease.

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The important role of Helicobacter pylori in idiopathic duodenal ulcer disease has been widely acknowledged since the clear demonstration that ulcer relapse or remission is strongly associated with H pylori colonisation or absence from the gastric mucosa.1–3 H pylori therapy is recommended in patients with relapsing duodenal ulcer disease, but a simple and safe treatment schedule is not yet available. Demand- ing oral triple therapy eradicates H pylori in up to 96% of patients treated4 but does have considerable side effects.5 6 Because of this there has been

Methods

Forty patients who qualified for admission to the study (Tables I and II) were randomly assigned to receive either omeprazole (20 mg twice daily) (Antra, Astra Chemicals, Wedel/Holstein, Germany) before meals and amoxicillin suspension (500 mg four times daily) (Amoxypen suspension, Grünenthal, Stolberg, Germany) before meals and at bedtime for two weeks (group I) or bismuth subsalicylate (600 mg three times daily) (Jatrox, Röhm Pharma, Weiterstadt, Germany) before meals, metronidazole (400 mg three times daily) (Clont 400, Bayer, Leverkusen, Germany) and tetracycline (500 mg three times daily) (Hostacyklin 500, Hoechst, Frankfurt, Germany) after meals, and ranitidine (300 mg at night) for two weeks (group II). After stopping the study medication all patients in both groups continued treatment with 300 mg ranitidine at bedtime for four weeks up to the final follow up examination.

Before starting treatment patients were talked to and were given an information sheet on the basic concepts of the pathophysiology of H pylori infection. They were then asked to participate after a full explanation of the aims and methods of the study, and all gave informed consent. During treatment, patients were asked to consult their study physician if they had side effects. In addition, complaints and side effects were recorded in a diary. Patient compliance was checked with a diary and by counting the number of returned tablets or by calculating the quantity of amoxicillin suspension used, respectively.

Before treatment and after six weeks, patients were investigated clinically, including a symptom score (grade 0: none, grade 1: mild, grade 2: moderate, grade 3: severe complaints due to peptic ulcer disease), and endoscopically. Four
Eradication of *Helicobacter pylori* with clarithromycin and omeprazole

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Abstract

Clarithromycin, a new and well tolerated, acid stable macrolide antibiotic, has a similar antimicrobial spectrum to erythromycin but a better in vitro MIC<sub>90</sub> (0·03 μg ml<sup>−1</sup>) against *Helicobacter pylori* (*H pylori*). This study aimed at determining the eradication rate using clarithromycin 500 mg thrice daily and omeprazole 40 mg daily for two weeks. Patients were given an endoscopy and *H pylori* status assessed by antral culture (microaerobic conditions, for up to 10 days), antral and corpus histology tests (haematoxylin and eosin/Gimenez stains), and 13C-urea breath test (13C-UBT, European standard protocol, positive result = excess δ<sup>13</sup>CO<sub>2</sub> excretion >5 per mil). Compliance was assessed by returned tablet counts. *H pylori* clearance at the end of treatment and eradication four weeks after finishing treatment were assessed by the 13C-UBT. Seventy three patients (54 men, median age 45 years) with duodenal ulcers (*n=42*) or duodenitis/non-ulcer dyspepsia (*n=31*) all with a positive 13C-UBT (mean (SEM) excess δ<sup>13</sup>CO<sub>2</sub> excretion=26.6 (4.9) per mil) and either positive antral histology (*n=72*) or positive antral culture (*n=35*) were studied. Before treatment 2/27 (7%) isolates of *H pylori* were resistant to clarithromycin and five isolates were resistant to metronidazole. In 70/73 (96%) the 13C-UBT was negative, initiated after finishing treatment. Four weeks later the 13C-UBT was negative in 57/73 (mean (SEM) excess δ<sup>13</sup>CO<sub>2</sub> excretion=1·2 (0·3) per mil, eradication rate=78%). Forty eight (66%) patients experienced a metallic taste while taking the tablets. Although four (5%) patients, however, could not complete the course of treatment, in only one of these four was *H pylori* not eradicated. These results show that dual therapy with clarithromycin and omeprazole is well tolerated. With an eradication rate of 78% it is an effective treatment for metronidazole resistant *H pylori* and may be an alternative to standard triple therapy.

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Eradication of *Helicobacter pylori* (*H pylori*) cures gastritis and prevents relapse of duodenal ulcer. There are several drawbacks, however, to the recommended two week triple therapy for eradicating *H pylori*. Bismuth salts, an important component of most regimens are not universally available, while failure of eradication therapy is often associated with pretreatment metronidazole resistant *H pylori*. Poor compliance with treatment because of side effects, frequent dosing, and the length of treatment is also a factor. Simpler and better tolerated regimens that contain neither bismuth nor metronidazole are needed.

Omeprazole, a H<sup>+</sup>/K<sup>+</sup> ATPase inhibitor, has been proposed as a suitable adjunct to *H pylori* treatment regimens for several reasons. It seems to suppress *H pylori* directly and to increase the antibacterial effectiveness of some antibiotics by increasing the gastric pH towards their negative logarithms of the acidic dissociation constant (pK<ac>). Omeprazole may also decrease the acid storage pool for weak base antibiotics (thus increasing the gastric mucosal concentration) and may decrease the rate of intragastric catalysis of the antimicrobial.

Clarithromycin (Abbott Laboratories, North Chicago, Illinois) is a new macrolide antibiotic (6-methoxy-erythromycin) with similar antimicrobial spectrum to erythromycin, but is more acid stable with fewer alimentary side effects. It has more predictable pharmacokinetics and has a half life of eight hours. Clarithromycin is used for the treatment of upper and lower respiratory tract infections and at doses of 2 g twice daily has been shown to be effective in HIV positive patients with *Mycobacterium avium* complex infections. In vitro its MIC<sub>90</sub> against *H pylori* is 0·03 μg ml<sup>−1</sup>. To develop a regimen that contains neither bismuth, nor metronidazole, we have assessed the effectiveness of a two week treatment with clarithromycin 500 mg thrice daily and omeprazole 40 mg in the morning in eradicating *H pylori*.

Patients and methods

After routine diagnostic upper gastrointestinal endoscopy, patients with known *H pylori* infection were invited to enter the study, which was approved by the Parkside ethical committee. The patients gave written informed consent. Patients with previous gastric surgery, known bleeding diathesis, penicillin allergy, or taking oral anticoagulants were excluded.

All endoscopes were disinfected after each examination using an automatic washing machine (Olympus EW20) and the biopsy forceps were sterilised by autoclaving.

ASSESSMENT OF *H pylori* STATUS

*H pylori* status was determined using the 13C-urea breath test (13C-UBT, see over) and histological examination (two antral biopsy specimens processed to paraffin wax, haematoxylin and eosin and Gimenez stains). Whenever possible, after initial isolation (two antral and two corpus biopsy specimens, selective and
The most cited papers in Gut: a decade of Helicobacterology

John Calam

Our most-cited papers covered a variety of subjects. The leading papers in 1987–1990 were on topics as diverse as ulcer complications of non-steroidal anti-inflammatory therapy (Armstrong et al 1987), mechanisms of lower oesophageal sphincter incompetence in reflux (Dent et al 1988), malignancy in coeliac disease (Holmes et al 1989), and cytokine expression in inflammatory bowel disease (Ligumsky et al 1990). However, the lion’s share of most cited papers went to *Helicobacter pylori*. This subject accounted for the leading papers in 1985, 1986 and 1992, and for all three of the most cited papers in 1991, 1993 and 1994. The account below summarises key aspects of *H pylori*, highlighting the findings reported in these papers.

Epidemiology

The prevalence of *H pylori* in the West rises with age and is greater in poorer persons. Sitia et al found this in men in Caerphilly.1 The prevalence rose abruptly from 30% in 30–34 year olds to 59% at >45 years of age. The rise with age is now attributed to a cohort of older persons who had greater exposure to *H pylori* in the past.2 *H pylori* might have been disseminated during the second world war. During the Gulf war, 7% of American servicemen acquired *H pylori* in six months,3 compared with an acquisition rate of 0.5% per annum in American civilians.4 In developing countries up to 80% of the entire population is infected in childhood.

Disease associations

The associations of *H pylori* with ulcers was shown by Price et al in 1985.5 The prevalence in patients with duodenal ulcers, gastric ulcers and normal endoscopy were 81%, 57% and 36%, respectively. Curious cigar-shaped bacteria seen on scanning electron microscopy of the antrum of patients with duodenal ulcer disease remain an enigma. More sensitive tests for infection now show even higher prevalences in ulcer disease, and gastric cancer of the intestinal type6 and gastric lymphomas1 have been added to the list of associated diseases. In 1994 Labenz et al7 nearly confirmed the association with gastric ulcer. When *H pylori* was eradicated, gastric ulcers healed more rapidly and only 3% relapsed during the first year, compared with 56% in the uneradicated. In 1991 Sobala presented a detailed account of his own first infection with this bacterium. He experienced gastrointestinal symptoms, endoscopy showed gastritis, secretion of acid and ascorbic acid into the gastric lumen were diminished and antibodies appeared in his blood.

Effects of *H pylori* infection on the stomach

Effects of *H pylori* on the gastric mucosa are of considerable interest in relation to the different disease outcomes and the possibility of immunisation against this infection. In 1986 Johnson et al reported that this bacterium only colonises gastric type epithelium.8 It was seen on patches of gastric metaplasia, but not elsewhere in the duodenum. It was absent from patches of intestinal metaplasia in the stomachs of infected persons.

By 1990 the variable behaviour of *H pylori* in bacterium–host interactions was attracting attention. Hessey et al9 found that patients in whom more bacteria were adherent to the mucosa showed greater epithelial degeneration, but less infiltration with polymorphs. The polymorphs might have been somehow preventing adhesion. In 1991 Crabtree et al10 reported the increased release of the cytokines tumour necrosis factor-a and interleukin-6 from infected biopsy specimens. Release of the latter was only increased in active gastritis. It is now clear that both the mucosal response to *H pylori* and the disease outcome depend significantly on the strain. The presence of circulating antibodies to the gene cagA indicates that the patient’s strain contains some or all of a “pathogenicity island” of genes which increase the risk of clinical disease.11 One of these genes, vacA, encodes *H pylori*’s vacuolating toxin. Variations in this gene’s signal sequence, which controls export of the toxin from the bacterium, also greatly affect the likelihood of peptic ulceration.12 Many individuals are infected with more than one strain of *H pylori*, which slightly complicates the issue.13

Previous thoughts on the aetiology of duodenal ulcer disease were based on the finding that these patients secrete more acid than controls. We now know that *H pylori* contributes to this by increasing release of the acid-stimulating hormone gastrin. Two highly cited papers from Moss et al14 and El Omar et al15 in 1993 provided evidence for this by showing for the first time that increased rates of basal and gastrin releasing peptide-stimulated acid secretion fall after eradication of *H pylori* from patients with duodenal ulcer. This mechanism presumably contributes to cure of duodenal ulcers by this approach.

Diagnosis

*H pylori* infection can be diagnosed at endoscopy by urease test, histology or by culture. In 1986 Rathbone et al16 reported an enzyme-linked immunosorbent assay (ELISA) which detected IgG and IgA antibodies to *H pylori* in
blood and IgA antibodies against the bacterium in gastric juice. This approach is now widely used in clinical practice and near-patient tests have been developed. The specificity and sensitivity of Helicobacter pylori ELISAs is being improved by use of mixtures of purified or recombinant antigens. A highly cited paper in 1994 reviewed another useful method—the urea breath test. This was invented simultaneously in Houston and Ipswich, and is highly accurate. It is the best test for determining the success or otherwise of eradication, so long as it is used at least four weeks after the end of treatment.

**Treatment**

Two highly cited papers claimed 75–80% eradication of *H pylori* with clarithromycin or amoxycillin (Labenz et al 1993) with a proton pump inhibitor (PPI) in dual therapies. The efficacy of the former has been confirmed, but the latter gives poor results in the UK. Nevertheless, these studies helped to establish the efficacy of clarithromycin and amoxycillin in combination therapy. Currently, the best regimens comprise a PPI given for one week with two of the three antibacterials: clarithromycin, amoxycillin and metronidazole. These regimens currently provide the optimal combination of efficacy, simplicity and low cost. The alternatives are currently too complex or expensive for routine use.

In 1992 the most cited paper was a review of the whole topic by Moss and myself. We were lucky to review such an interesting and important subject!